

Oral Synthetic Folic Acid and Vitamin B₁₂ Supplements Work—If One Consumes Them

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Oral supplements of synthetic folic acid and vitamin B₁₂ are very effective in increasing blood levels of the vitamins and are known to prevent birth defects and cardiovascular diseases.

Key words: folate, vitamin B₁₂, dietary supplements

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Introduction

In common practice, it is difficult to have more than 50% of the target population consume vitamin supplements, which suggests that fortification of a centrally processed and widely consumed food product would usually prevent more disease in a population than a supplement program. Fortification programs also cost much less than supplement programs.

More effective supplement programs may be developed that reach a greater number of women of reproductive age, such as combining folic acid with contraceptive pills. Supplement programs targeted at women of reproductive age will not benefit older members of the population.

Centrally processed foods in all countries should be fortified to prevent serious birth defects (and folate deficiency anemia and heart attacks and strokes) by providing the average woman of reproductive age with 400 μg of synthetic folic acid. Unless there are prior data suggesting a change, folic acid fortification should be at 250 μg per 100 g of grain or 2.5 ppm. Subsequent data may suggest a need to change the concentration. If so, the fortification concentration can be rapidly and easily changed by simply using a different vitamin premix.

It is reasonable to fortify a centrally processed food with vitamin B₁₂, as it is likely to prevent a large proportion of pre-clinical vitamin B₁₂ deficiency, delay the onset of clinical pernicious anemia and reduce ho-

mocysteine concentrations. Unless there are prior data suggesting a change, vitamin B₁₂ fortification should be at 10 μg per 100 g or 0.1 ppm of grain—a level that in many countries would provide the median person 15 μg of vitamin B₁₂ a day.

PAHO Fortification Role Model for World

Increasing folic acid consumption through sustainable fortification of centrally processed and widely consumed foods holds great potential for immediately improving health and nutrition for millions of the world's people.^{1–3} Folic acid fortification of flour and other grains in the U.S. and in Canada in the 1990s resulted in significant reductions in spina bifida and anencephaly—two common and serious birth defects.^{4,5} Less well appreciated is that these fortification programs also virtually eliminated folate deficiency anemia, a benefit that has yet to be quantified.^{6,7} In addition, these fortification programs lowered the population serum and plasma homocysteine concentrations so much that current studies in the U.S. seeking to examine the effect of lowering homocysteine on cardiovascular disease may be negative, because there simply are not enough people with sufficiently increased homocysteine levels to see a protective effect.^{8,9} The current literature suggests that the reduction of homocysteine caused by folic acid flour fortification prevents 10 times as many adults from dying from strokes and heart attacks as the fortification prevents birth defects.¹⁰ So far, studies have not been published which document the post-fortification impact on cardiovascular disease.

PAHO has been a leader in providing technical information associated with the implementation of folic acid fortification programs in an increasing number of Central and South American countries. This contribution has significantly improved health in these countries. In fact, it is Chile that has implemented the most rational and comprehensive fortification program.¹¹ Given that the current consensus is that all women who could get pregnant should consume 400 μg of synthetic folic acid to prevent birth defects, Chile instituted fortification at a concentration (220 μg per 100 g or 2.2 ppm) that was estimated to provide the median woman 400 μg of

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synthetic folic acid a day.^{12,13} The fortification concentration chosen in the U.S. was estimated to provide the median woman only 100 μg a day.¹⁴ If WHO and its other regions were to be as effective as PAHO has been, there would be 250,000 fewer children born each year with folic acid-preventable birth defects. The science and technology exists for WHO to provide the leadership that would result in the total prevention of folic acid-preventable birth defects by 2010.³

Having been such a leader in both iron and folate flour fortification, PAHO continues its leadership by providing an opportunity to examine the scientific rationale for vitamin B₁₂ fortification, and to make recommendations for fortification criteria. Optimally, future recommendations for vitamin B₁₂ should be made by determining how much vitamin B₁₂ is needed, and then recommending a fortification level that would have at least the median person consuming the recommended amount of vitamin B₁₂. In trying to standardize recommendations for fortification, some have suggested fortification criteria that would seek to provide the median person a percentage of the RDA for the fortificant. Although the science that is used to determine RDAs is available to all, the RDAs developed for countries can vary by 400%. Using RDAs, rather than the micrograms desired per day, leaves open the possibility of confusion by country level, policy makers and implementers, which in turn, could limit the benefits of a fortification program.

Folic Acid Supplements Effective in Preventing Birth Defects

Spina bifida and anencephaly are serious birth defects that Wald and his colleagues found could be prevented by taking oral synthetic folic acid supplements.¹⁵ In this study, the dose of synthetic folic acid was 400 μg in a pill. About a year after study, the U.S. Public Health Service (PHS) recommended that all women consume 400 μg of folic acid a day.¹² Although we at CDC assumed it would be clear that we were talking about 400 μg of synthetic folic acid above the folate in the usual diet, many were confused because we did not use the word “synthetic” in the recommendation. The 1998 Institute of Medicine cleared up the point by recommending that all women of reproductive age consume 400 μg of synthetic folic acid plus a diet rich in natural folates.¹³

At the time that the PHS recommendation was made, there were no studies using 400 μg of synthetic folic acid without other vitamins. CDC conducted a study in China in which women consumed only a supplement of 400 μg of oral synthetic folic acid without any other dietary intervention. As reported by Berry and colleagues, consumption of 400 μg of synthetic folic acid was very successful in lowering rates of spina bifida and anencephaly pregnancies.¹⁶ In the north of China,

there was an 85% reduction, which suggested that there existed in northern China a tenfold epidemic. This conclusion was determined by the fact that previous rates of spina bifida and anencephaly pregnancies were approximately 5 per 1000 pregnancies, which shrunk to about 0.5 per 1000 after synthetic folic acid consumption. In the south of China, where the previous rates were one per thousand, post-supplementation rates were reduced to about 0.5 per 1000. This also suggested that the epidemic in the South was a twofold increase. The China study showed that women who consume just 400 μg of synthetic folic acid have a remarkable reduction in risk for NTD pregnancies. This suggests that 400 μg of synthetic folic acid is highly effective at reducing almost all, if not all, of the risk for having folic acid-preventable spina bifida and anencephaly in at-risk populations when consumed.

A corollary of these data is that if the prevalence of spina bifida and anencephaly pregnancies is greater than 0.5 per 1000 births, it is an indicator of population-wide folate deficiency. The higher the rate above 0.5 per 1000 births, the greater the population folate deficiency. Given the difficulties in counting spina bifida and anencephaly in induced abortions of fetuses known to be affected with these birth defects, one should not so readily conclude that if the rates are less than 0.5 per 1000 births, that there is no folate deficiency in the population. Whereas excellent and costly surveillance systems may make such an inference possible, the large birth certificate system in the United States misses all the abortions induced because the fetuses were known to be affected with these birth defects; therefore, the observed rates below 0.5 per 1000 in that data set cannot be interpreted that there is no folate deficiency in the population.

Supplement Programs Reach Only Half the Population

If taken before and during the early weeks of pregnancy, folic acid supplements prevent birth defects. The problem with supplement use is that in the usual, workaday world, it is very difficult to get more than 50% of women to consume a supplement. The United Kingdom and the Netherlands, rather than implement a flour fortification program, implemented a public health campaign seeking to increase the number of women consuming folic acid containing vitamin supplements.^{17,18} Before the campaigns, use of supplements was about 10%. After the campaigns, usage rose to about 40%. The CDC and the March of Dimes in the U.S. have conducted programs to promote increased supplement consumption; however, these programs resulted in only 25% of pregnant women reporting consumption of folic acid supplements before pregnancy.¹⁹ Except in expensive and well-conducted research environments like the China study, supplement

programs leave at least half the target group without protection. This repeatedly observed ceiling of 50% or less coverage for supplement programs is a very strong argument for fortification programs. In countries where flour or other fortification is not possible, or the concentration required in grains is too low, as in the United States and Canada, supplement programs can help to decrease birth defects. Supplement programs should be seen as a complement—not a substitute—for fortification programs. In addition, the effectiveness of supplement programs needs to increase. Another potential method is the addition of folic acid to contraceptive pills. In a CDC study conducted in family planning clinics in Georgia, only 17% of the women were consuming folic acid supplements, while 43% were using oral contraceptives.²⁰ Among women attending these clinics, folic acid supplement use would have increased nearly threefold if the women using oral contraceptives had been taking oral contraceptives with 400 μg of synthetic folic acid.

It has been shown that folate deficiency is widespread among both male and female adults in all countries where it has been studied in the last decade. Therefore, another disadvantage of a supplement strategy targeted only to women is that it will not increase serum folates and prevent folate deficiency anemia for other adults in the population.^{21,22} These programs would not lower homocysteine and prevent cardiovascular disease among older adults.

Supplements Containing Folic Acid and Vitamin B₁₂ Consumed by Older Adults Reduce Homocysteine Concentrations and Raise Serum Folate and B₁₂ Concentrations

Americans are vitamin supplement consumers. In addition, the older a person is, the more likely he or she is to use a simple multivitamin preparation containing 400 μg of synthetic folic acid and 6 μg of synthetic vitamin B₁₂. In the 1988–89 examination of the Framingham cohort, 20% took supplements with folic acid and 29% consumed supplements with vitamin B₁₂.²³

Studies from Framingham note that a substantial proportion of the cohort had serum B₁₂ levels less than 258 pmol/L.²³ These people did not have the classical signs and symptoms of clinical B₁₂ deficiency associated with pernicious anemia. Carmel has called this “pre-clinical B₁₂ deficiency” because the subjects did not have overt anemia or neurological disease.²⁴ Although common, it remains uncertain as to whether or not treatment would improve the health of these people.

The widespread use of vitamin supplements permitted the opportunity to see if six micrograms of vitamin B₁₂ can be effective in increasing serum B₁₂ and reducing homocysteine and methyl malonic concentrations in older people. In short, they are very effective. For ex-

ample, 40% (160/401) of the total Framingham study had serum B₁₂ less than 258 pmol/L.²³ It reached 49% for those not taking supplements (141/286) but was reduced to 16% (19/115) for those consuming supplements. Therefore, it is clear that 6 μg of synthetic B₁₂ a day is very effective in reducing the proportion with low serum B₁₂ in this elderly cohort. If you don’t take a supplement, you are 300% more likely to have pre-clinical B₁₂ deficiency.

Methyl malonic acid (MMA) increases when there is tissue level B₁₂ deficiency. In the Framingham cohort, 14% were determined to have an elevated MMA. The rate in those not taking supplements (20% or 48 of 238) was three times higher than those taking B₁₂ containing supplements (7% or 8 of 107).

Thus, there are strong data that elderly people who consume 6 μg of synthetic vitamin B₁₂ can reduce by two-thirds the proportion with low vitamin B₁₂ concentrations and increased MMA concentrations. Feeding studies of persons with pre-clinical B₁₂ deficiency have shown that a proportion will need more than 6 μg a day.²⁵

Post-Folic Acid Fortification in United States Shows Multivitamin Supplement Consumers Consume Enough Folic Acid and Vitamin B₁₂

Jacques and colleagues examined the children of the participants of the original Framingham cohort before and after folic acid fortification in the United States. They found among those subjects *consuming* multivitamins with folic acid and vitamin B₁₂ that folic acid fortification did *not* lower homocysteine concentrations.⁹ This finding is consistent with studies in the original Framingham cohort, and suggests that adults taking supplements did not need more folic acid to lower their homocysteine concentration. Their homocysteine levels were already sufficiently lowered by the supplement. On the other hand, the 70% of the cohort *not* consuming folic acid– and vitamin B₁₂–containing supplements had a remarkable reduction in homocysteine concentrations merely from consuming folic acid–fortified products. They needed more folic acid consumption. The post-fortification homocysteine concentrations in the non-supplement taker group was, however, *not* as low as the supplement consumer before folic acid fortification. These data suggest that multivitamin supplement consumers are consuming something that non-supplement consumers are not getting in flour fortified with folic acid. The obvious difference is that flour has yet to be fortified with vitamin B₁₂. Fortification with vitamin B₁₂ would have likely further reduced homocysteine concentrations in the non-supplement consuming group. Consumers of supplements were also consuming more folic acid, which suggests that increasing the concentration of

folic acid in enriched grains in the U.S. would also further reduce homocysteine concentrations.

Folic Acid and Vitamin B₁₂ Supplements Associated with Prevention of Cardiovascular Disease

There is a large body of evidence, including randomized controlled trials, suggesting that consuming folic acid and supplements containing vitamin B₁₂ will substantially decrease the risk of heart attacks and strokes.^{26,27} Mark and associates reported a randomized controlled trial showing that a multivitamin supplement prevented strokes.²⁸ More recently, Wald and colleagues have looked at Mendelian randomization and concluded that approximately 25% of strokes and heart attacks can be prevented by increasing consumption of folic acid.¹⁰ These data suggest that the number of deaths from cardiovascular disease prevented by folic acid fortification will be approximately 10 times the number of infants that will not have birth defects because of fortification.

Priorities for Fortification

The recent addition of folic acid, but not vitamin B₁₂, to flour and other “enriched” grain products in the U.S. and Canada has been associated with remarkable reductions in birth defects, folate deficiency anemia and reduction in the concentration of serum homocysteine.^{4–6,9} Thus folic acid fortification deserves the highest priority worldwide. Although it has yet to be demonstrated that fortification of flour with vitamin B₁₂ will improve the health of the population, it seems very likely that such fortification would prevent much of “pre-clinical” vitamin B₁₂ deficiency, would delay the onset of neurological symptoms in persons destined to have clinically apparent pernicious anemia, and would make a small contribution to reducing serum homocysteine concentrations. Given the great known advantage of folic acid fortification, folic acid fortification should not be delayed for extensive discussions regarding whether or not to fortify with vitamin B₁₂. The Americas have clearly shown that flours fortified with folic acid—and not fortified with vitamin B₁₂—are safe, and prevent important diseases.

What Concentrations to Fortify Flour with Folic Acid and B₁₂

The 1998 IOM report suggests that all persons over 50 consume 2.4 μg of synthetic vitamin B₁₂ because of widespread mild, pre-clinical vitamin B₁₂ deficiency among the elderly.¹³ Given the great exposure to 6 μg per day in the U.S. and the data from studies of the Framingham cohorts, 6 μg per day seems appropriate. The recent feeding studies of some elderly people with

pre-clinical B₁₂ deficiency suggests that a proportion will need to consume more than 6 μg a day to prevent pre-clinical vitamin B₁₂ deficiency.²⁵

It would seem reasonable to have flour fortified with vitamin B₁₂ in order to assure that most people consumed at least the 2.4 μg of synthetic B₁₂ that the IOM recommended. If fortification concentrations were set so that the median person consumed 6 μg of synthetic vitamin B₁₂ a day, most of the population would be consuming 2.4 μg a day. Since the feeding data suggest that some will need more, the default B₁₂ fortification concentration in flour should be 10 μg per 100 g of grain or 0.1 ppm. Where flour is consumed at approximately the rate it is consumed in the U.S., the median person would consume about 15 μg a day. This level of consumption would prevent a great deal of the pre-clinical B₁₂ deficiency. Because it will be consumed on a chronic basis while intrinsic factor is active, those who lose intrinsic factor may have a delay in the onset of their clinical pernicious anemia.

The United Kingdom Committee on the Medical Aspects of Food and Nutrition Policy recommended mandatory fortification of flour at 240 μg of synthetic folic acid per 100 g of grain (2.4 ppm).²⁹ Chile has successfully and safely fortified with 220 μg of synthetic folic acid per 100 g of grain (2.2 ppm). Australia and New Zealand permit fortification at 280 μg of synthetic folic acid per 100 g of grain (2.8 ppm).³⁰ Folic acid is safe, and the benefit from fortification is so great to both children and adults that it is important for public health to implement fortification programs as quickly as possible.³¹ The standard for folic acid fortification should therefore be 250 μg of synthetic folic acid per 100 g of grain (2.5 ppm), unless there are existing data in a country that suggest it should be set lower or higher. If new data become available after fortification is implemented that suggest a change is needed, the change can be quickly implemented; millers will only need to change the kind of pre-mix they are using. Changing the pre-mix can be done in a single day.

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Dr. Oakley is a co-inventor on a patent that covers putting folic acid in oral contraceptives. If compensated for this invention, it would be under the rules of the U.S. Centers for Disease Control and Prevention. He is a consultant to Johnson and Johnson on this issue.

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