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# Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects

U.S. Department of Health and Human Services Public Health Service Centers for Disease Control Atlanta, Georgia 30333

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Contents

Introduction Recommendations Comment References

Recommendations for the Use of Folic Acid to Reduce the Number of Cases of Spina Bifida and Other Neural Tube Defects

Summary

Spina bifida and anencephaly are common and serious birth defects. Available evidence indicates that 0.4 mg (400 ug) per day of folic acid, one of the B vitamins, will reduce the number of cases of neural tube defects (NTDs). In order to reduce the frequency of NTDs and their resulting disability, the United States Public Health Service * recommends that:

All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs. Because the effects of higher intakes are not well known but include complicating the diagnosis of vitamin B((12)) deficiency, care should be taken to keep total folate consumption at less than 1 mg per day, except under the supervision of a physician. Women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice.

INTRODUCTION

Each year in the United States about 2,500 infants are born with the neural tube defects (NTDs) spina bifida and anencephaly. In addition, an unknown number of fetuses affected by these birth defects are aborted. All infants with anencephaly die shortly after birth, whereas the majority of babies born with spina bifida grow to adulthood with, in severe cases, paralysis and varying degrees of bowel and bladder incontinence. The evidence that consumption of folic acid, one of the B vitamins, before conception and during early pregnancy (the periconceptional period) can reduce the number of NTDs has been accumulating for several years. Published data are available from randomized controlled trials (1,2), nonrandomized intervention trials (3,4), and observational studies (5-8) (Tables 1 and 2, Figure 1).

One of the most rigorously conducted studies was the randomized controlled trial sponsored by the British Medical Research Council (MRC) (2). The study showed that high-dose folic acid supplements (4.0 mg per day) used by women who had a prior NTD-affected pregnancy reduced the risk of having a subsequent NTD-affected pregnancy by 70%.

Preliminary results from the Hungarian randomized controlled trial of multivitamin/mineral supplementation (including 0.8 mg of folic acid) among women who had not had a prior NTD-affected pregnancy were reported in 1989 (9). This trial was stopped in May 1992 on the advice of an ad hoc scientific advisory committee because of evidence of an NTD-protective effect of the multivitamin/mineral preparation relative to the study placebo preparation (Czeizel AE: personal communication, May 1992).

Three of four published observational studies showed a lowered risk of NTDs for women who have not had a prior NTD-affected pregnancy and who consumed 0.4-0.8 mg (400-800 ug) of folic acid daily from multivitamin supplements (Tables 1 and 2, Figure 1).

In summary, the data available indicate that folic acid can help avert NTDs when given at high-dose levels (i.e., 4.0 mg per day). The results of the British MRC study showed that the addition of other vitamins to 4.0 mg of folic acid confers no extra benefit in averting NTDs. Based on a synthesis of information from several studies, including those which used multivitamins containing folic acid at a daily dose level of greater than or equal to 0.4 mg, it was inferred that folic acid alone at levels of 0.4 mg per day will reduce the risk of NTDs. The protective effect found in the studies of lower-dose folic acid, measured by the reduction in NTD incidence, ranged from none to substantial (Tables 1 and 2, Figure 1); a reasonable estimate of the expected reduction in the United States is 50%. Thus there appear to be excellent prospects for substantially reducing the number of NTDs among U.S. women who have not had a prior NTD-affected pregnancy through the use of folic acid at intakes of approximately 0.4 mg daily.

RECOMMENDATIONS

Available evidence indicates that 0.4 mg (400 ug) per day of folic acid, one of the B vitamins, will reduce the number of cases of NTDs. In order to reduce the frequency of NTDs and their resulting disability, the United States Public Health Service recommends that:

All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs. Because the effects of high intakes are not well known but include complicating the diagnosis of vitamin B((12)) deficiency, care should be taken to keep total folate consumption at less than 1 mg per day, except under the supervision of a physician. Women who have had a prior NTD-affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice.

COMMENT

The possibility for reducing by 50% the number of cases of spina bifida and other NTDs in the United States through daily consumption of 0.4 mg of folic acid presents an important opportunity in public health. Efforts are now being made by the PHS to assure that all women capable of becoming pregnant consume 0.4 mg of folic acid daily to achieve this goal.

There are three potential approaches for the delivery of folic acid to the general population in the dosage recommended: a) improvement of dietary habits, b) fortification of the U.S. food supply, and c) use of dietary supplements. The Food and Drug Administration (FDA) will have to determine which approaches will best achieve the goal of increasing folic acid intake while ensuring that potential risks created by overfortification of food with folic acid, and thus overconsumption of this substance, are not reached. This process will require rulemaking and will include substantial efforts to involve the obstetrics community, other medical groups, the scientific community, consumers, industry, and other PHS agencies in a search for the best way to accomplish this goal. While this process is under way, and before the FDA issues final regulations on food fortification and permissible health claims on food labeling, further food fortification with folic acid would be inappropriate, and no health claims should be made.

Folate intake greater than or equal to 0.4 mg per day can be obtained from the diet through careful selection of foods. Folate is a generic term for food compounds that have the biologic activity of folic acid; in general, folates obtained from foods are not as well absorbed as is folic acid. Although the average consumption of dietary folate by women in the United States has been estimated to be about 0.2 mg per day (10), women who select foods consistent with the U.S. Dietary Guidelines for Americans and the U.S. Dietary Pyramid are likely to consume diets containing greater than or equal to 0.4 mg of folate daily. Use of currently available fortified foods, such as some breakfast cereals, can also provide important sources of folic acid.

Folic acid supplement pills containing 0.4 mg of folic acid also are available, as are multivitamin preparations containing folic acid. About 20% of U.S. women now consume multivitamin preparations, which generally contain 0.4 mg of folic acid (11). Supplements for pregnant women generally contain up to 0.8 mg of folic acid.

Given these alternative routes for obtaining adequate amounts of folic acid, it is recommended that women be advised of the options available to them to obtain daily intakes of 0.4 mg of folic acid and be encouraged to meet this goal.

The research that serves as the basis for this recommendation generally focused on the use of supplements from at least 1 month before conception through early pregnancy, the periconceptional period. Development of the defect in the neural tube occurs within the first month after conception, before most women are aware of their pregnancy. Because greater than 50% of pregnancies in the United States are unplanned (12), it would be prudent for women to consume 0.4 mg of folic acid daily on a regular, continuous basis as long as they are capable of becoming pregnant.

Because supplements containing folic acid at the 0.4-mg level are widely available, this dosage has been the focus of the available observational research studies. It is possible that lower doses of folic acid may reduce the

risk for NTDs, but further research would be needed to learn the minimum effective dose.

At this time, FDA allows food to be labeled according to the level of nutrients in the food relative to the U.S. Recommended Daily Allowances (USRDAs). Consumption of folic acid at USRDA-level doses (0.4 mg for nonpregnant women) is considered a safe and desirable practice. Over the years, RDAs have ranged from 0.18 to 0.4 mg of folic acid for women of childbearing age. RDAs for pregnant women have ranged from 0.4 to 0.8 mg per day. Folic acid is a water-soluble vitamin, and any excess consumed is rapidly excreted in the urine. The effects of higher doses are not well known, although they include complicating the diagnosis of vitamin B((12)) deficiency in certain people (13). Irreversible neurologic damage may occur if B((12)) deficiency is not diagnosed and treated. Therefore, women should be careful to keep their total daily folate consumption at less than 1 mg per day. Women may wish to consult their physicians or other health-care providers (nutritionists, dietitians) about how to best obtain the recommended amount of folic acid, while avoiding excessive consumption. Caution should also be taken to prevent excessive use of multivitamin supplements or fortified foods containing vitamin A, since excess vitamin A may cause birth defects. Further research will be needed to identify any unknown adverse effects.

It is expected that consumption of adequate folic acid will avert some, but not all, NTDs. The underlying causes of NTDs are not known. Thus it is not known what proportion of NTDs will be averted by adequate folic acid consumption. From the available evidence, CDC estimates that there is the potential for averting 50% of cases that now occur. However, until further research is done, no firm estimate of this proportion will be available. Moreover, further research will be needed to identify the causes of NTDs that are not averted by folic acid intake.

The current recommendation is directed to all U.S. women, including women who have had a previous NTD-affected pregnancy. In August 1991, CDC issued a guideline (14) for women who have had a prior pregnancy affected by NTDs and who are planning to start a new pregnancy. The guideline called for the consumption of a 4.0- mg daily dose of folic acid, from at least 1 month before conception through the first 3 months of pregnancy. The guideline did not specifically address the issue of folic acid consumption among these women during the times when they are not planning to become pregnant. Women who have had an NTD-affected pregnancy should consume 0.4 mg of folic acid per day, unless they are planning a pregnancy. When these women are planning to become pregnant, they can follow the August 1991 guideline and consult their physicians about the desirability of using 4.0 mg of folic acid per day. Because 4.0 mg of folic acid per day is a very high dose, there may be risks associated with these levels. Although it appears that a lower dose, such as 0.4 mg, may have as great a beneficial effect as 4.0 mg, women who are at very high risk of having an NTD-affected pregnancy may choose to follow the August 1991 guideline a) because it is based on data from the most rigorous study directly pertinent to their risk of NTDs, and b) because their risk of having an NTD-affected pregnancy may outweigh any risk that may occur as the result of the use of 4.0 mg of folic acid.

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