# Folic Acid Protects Against Some Birth Defects

One of the most exciting scientific developments in the past several decades is the finding that folic acid (one of the B vitamins) plays a critical role in protecting against neural tube birth defects (NTDs) such as spina bifida when taken by women of childbearing age before conception and during early pregnancy. Most of the clinical evidence is from studies using *multivitamins containing folic acid*, rather than the use of folic acid alone.

NTDs are very serious defects that occur in the United States and Canada in about one of every thousand births. Higher rates of incidence occur in Great Britain and Ireland and in northern Chinese populations. NTDs include conditions such as spina bifida (a failure of closure of the neural tube surrounding the spinal cord) and anencephaly (partial absence of the brain). Babies with spina bifida generally survive, but may require extensive surgical and medical care and may be permanently disabled. Babies with anencephaly do not survive.

Nutritional status is a key component affecting the occurrence of neural tube defects. Some studies have shown that women with higher dietary folate intakes had a lower risk of having a baby with an NTD. In other studies, women who took multivitamins containing folic acid had a lower risk of having a baby with an NTD than women who did not take multivitamins. These studies showed that it was critical that the supplement be used at least a month before conception and during at least the first month following conception. The neural tube of the fetus closes (or tragically fails to close) in the first month of pregnancy, at a time when many women are not yet aware they are pregnant.

In the U.S., approximately 3000 pregnancies are affected by NTDs each year, and worldwide these birth defects affect 300,000 or more pregnancies annually. (Berry, Li, et al., 1999; CDC, 2009) Scientific evidence makes it clear that supplementation with a multivitamin containing folic acid could prevent a large fraction of these defects.

### Food Folate vs Folic Acid

Folate is the form of this B vitamin that occurs naturally in foods. It must be modified by an enzyme in the intestine before it can be absorbed. Only about half the folate in foods is absorbed.

Folic acid is the synthetic form of this B vitamin that is used in nutritional supplements, fortified foods, and clinical trials.

It is very efficiently absorbed by the body.

## NOTE ON ABBREVIATIONS

The recommended daily quantity of folic acid for women of childbearing age is 400 micrograms per day (equivalent to 0.4 mg per day). The abbreviation of the term "microgram" for purposes of nutrition labeling is "mcg," while the scientific abbreviation is "µg." In this document we will use the abbreviation "mcg."

## RECOMMENDATION OF THE PUBLIC HEALTH SERVICE

In 1992, the U.S. Public Health Service considered the available evidence and recommended 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." (CDC, 1992)

## RECOMMENDATION OF THE FOOD AND NUTRITION BOARD

In its 1998 report on recommendations for the B vitamins, the Food and Nutrition Board of the Institute of Medicine outlined the evidence relating to folic acid and neural tube defects. (Institute of Medicine, 1998) A number of scientific studies have shown that women who took a folic acid supplement of 360 to 800 mcg per day, *in addition to their usual diet* providing 200 to 300 mcg of dietary folate per day, had a reduced risk of having a baby with a neural tube defect.

In addition to protecting against neural tube defects such as spina bifida, multivitamins and fortified foods containing folic acid have been shown in some studies to prevent other types of birth defects, including cleft palate and cleft lip and some cardiovascular malformations, according to the Food and Nutrition Board.

Based on this evidence, the Food and Nutrition Board issued new dietary recommendations for folic acid in 1998, recognizing the need for women of childbearing age to get *supplemental folic acid***,** over and above the amounts that are naturally present in foods. (Institute of Medicine, 1998)

### Recommendation for Women Capable of Becoming Pregnant

The Food and Nutrition Board of the Institute of Medicine recommends "that women capable of becoming pregnant consume 400 mcg of folate daily from supplements, fortified foods, or both in addition to consuming food folate from a varied diet. At this time the evidence for a protective effect from folate supplements is much stronger than that for food folate."

## FDA HEALTH CLAIM AND MANDATORY ENRICHMENT

In 1996, FDA concluded that the evidence was strong enough to support a health claim that may be used in the labeling of foods and dietary supplements containing the B vitamin folic acid. The claim may state that "healthful diets with adequate folic acid may reduce a woman's risk of having a child with a brain or spinal cord birth defect." (FDA, 1996a)

Beginning in 1998, FDA required that folic acid be included among the nutrients added to enriched grain products such as flour, breads, and pasta. Previously, only iron, thiamin, riboflavin, and niacin were added to enriched grain products. The level of folic acid fortification is relatively modest (140 mcg per 100 grams of product), about twice the level of folate that is naturally present in whole wheat. (FDA, 1996b)

The level of folic acid fortification selected by FDA was initially expected to deliver an additional 80 to 100 mcg of folic acid to the daily diets of women of childbearing age, but the actual increase in the amount consumed appears to be higher than that, and blood levels of folate have increased substantially. CDC has documented a decline of 26 percent in the incidence of NTDs since mandatory enrichment—a very important

gain, even if it does not match the impact that would be predicted if women got the full recommended amount of supplemental folic acid. (CDC, 2004)

An analysis of folic acid intake in the 2003-2006 National Health and Nutrition Examination Survey found that 42 percent of adults consumed folic acid only from enriched grain products and not from ready-to-eat cereals or supplements; 18 percent consumed both enriched grains and ready-to-eat cereals; 25 percent consumed ready-to-eat cereals and dietary supplements containing folic acid; and 15 percent consumed all three sources of folic acid. The usual amount of folic acid consumed by the four groups was 138, 274, 479, and 635 mcg per day, respectively. (Yang, Cogswell, et al., 2010) Clearly, most people who do not consume folic acid supplements are not reaching daily intakes of 400 mcg per day.

## ISSUES RELATING TO MANDATORY ENRICHMENT

Because of the closely inter-related functions of folic acid and vitamin B-12, there is continuing concern about the significance of raising population intakes of folic acid without also raising population intakes of vitamin B-12, and there is discussion of the possibility of adding vitamin B-12 to the enrichment package. (Green, 2009) Also, there is controversy about the potential effect of folic acid enrichment on the progression of some cancers, especially colorectal cancer. Folate is required for cell division and growth. This applies to cancer cells as well as to healthy cells, and antifolate drugs are used in cancer treatment. It has been suggested that folic acid supplementation may help protect against the initiation of cancer, but may facilitate the growth or progression of precancerous cells once they are present. (Mason, Cole, et al., 2008; Smith, Kim, et al., 2008) However, recent analysis of a very large cohort of over 500,000 people found that higher folic acid intakes from diet or from supplements were associated with a decreased risk of colorectal cancer, and this association was similar in the periods before and after mandatory enrichment. (Gibson, Weinstein, et al., 2011) There will be ongoing monitoring and research to clarify the impact of enrichment on all segments of the population.

## RECOMMENDATION OF THE U.S. PREVENTIVE SERVICES TASK FORCE

In 2009, the U.S. Preventive Services Task Force reviewed and reiterated its recommendation that "all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid." This is classified as a grade A recommendation. (U.S. Preventive Services Task Force, 2009) The purpose of this recommendation is to reduce the risk of having a baby with a neural tube birth defect. According to the Task Force, these birth defects, which include spina bifida, are the most common birth defects in the U.S., occurring in about one in every 1000 pregnancies.

## CDC RECOMMENDATION FOR CONTINUED EMPHASIS ON SUPPLEMENTATION

According to a CDC report on a 2007 Gallup survey of folic acid supplement knowledge and use, most women were aware of folic acid, but less than half of women of childbearing age reported daily consumption of a supplement containing folic acid. Young women (age 18 to 24) were least likely to be using such a supplement. According to the report, "These findings warrant the continued promotion of folic acid consumption among all women of childbearing age and especially among women aged 18-24 years. Folic acid education that promotes consumption of folic acid from various sources (e.g., supplements containing folic acid and fortified foods), in addition to foods rich in folate, can increase the possibility of all women consuming the recommended amount of 400 mcg." (CDC, 2008)

## KEY CLINICAL TRIALS

The evidence on folic acid and birth defects began developing in England in the early 1980s, when Dr. R. W. Smithells and coworkers, in a multicenter clinical trial, gave a multivitamin supplement containing folic acid to women who had already had a previous pregnancy affected by an NTD and who wanted to become pregnant again. The multivitamin provided 360 mcg (0.36 mg) of folic acid per day. The rate of recurrence of NTDs in the supplemented group was one percent, compared to five percent in women who did not receive a supplement. The protective effect was thus an 80 percent reduction in the incidence of NTDs. (Smithells, Nevin, et al., 1983; Smithells, Sheppard, et al., 1980)

Smithells' study was a carefully conducted clinical trial, but it was not a randomized placebo-controlled trial, since the institutional review board overseeing the research would not allow any of the women to be given a placebo instead of the multivitamin. To definitively confirm or refute these results, and to determine whether folic acid was the nutrient responsible for the reduction in NTDs, a large, multicenter, randomized controlled trial was initiated in 1983 by the U.K. Medical Research Council.

**...all women planning pregnancy should receive a vitamin supplement containing folic acid.**

In 1991, the Medical Research Council reported that a supplement of 4 mg (4000 mcg) of folic acid had a protective effect of 72 percent against the recurrence of NTDs in 1,195 women who had already experienced at least one affected pregnancy. The relatively high dose of folic acid was chosen to assure that any beneficial effect would be found and not missed because of too low a dose. The degree of protection was similar to that achieved by Smithells' use of a low level of supplementation (0.36 mg of folic acid in a multivitamin). There were 21 NTDs in 602 pregnancies in the control groups, and six NTDs in 593 pregnancies in the supplemented groups. The researchers concluded that "public health measures should be taken to ensure that all women of childbearing age receive adequate dietary folic acid." (MRC Vitamin Study Research Group, 1991)

Another randomized controlled trial was initiated in Hungary in 1984, when a multivitamin supplement containing folic acid (0.8 mg) or a placebo was offered to Hungarian women planning a pregnancy as part of the Hungarian Family Planning Program. By the time the study was concluded in 1991, there had been about 2,000 pregnancies in the supplement group and about the same number in the control group. There were no NTDs in the supplement group, compared to six in the placebo group. In addition, there were fewer malformations of all types in the supplement group compared to the placebo group (13 per 1,000 pregnancies, compared to 23 per 1,000). The researchers concluded: "Given the results of this study, we think that all women planning pregnancy should receive a vitamin supplement containing folic acid." (Czeizel & Dudas, 1992)

A public health program in China was undertaken from 1993 to 1995 in which women were asked to take a supplement of 400 mcg of folic acid daily from the time of their premarital medical examination until the end of their first trimester of pregnancy. The program involved almost 250,000 women. In the northern region of China, where there is a high incidence of NTDs, there were about five neural tube defects per 1,000 births among women who did not receive the supplement. This was reduced to one per 1,000 (a reduction of 80 percent) among women who were supplemented. In the southern region of China, the rate of NTDs was much lower—about one per 1,000 births for unsupplemented women. This was reduced to 0.6 per 1,000 births (a reduction of about 40 percent) in women who received the supplement. This study demonstrates that folic acid supplementation helps prevent NTDs in areas of high incidence as well as in areas of low incidence. (Berry, Li, et al., 1999)

Another study in 18 counties of China confirmed the effectiveness of a multivitamin with folic acid in reducing the incidence of NTDs. Incidence was 0.35 per 1,000 pregnancies in the multivitamin group and 1.8 per 1,000 pregnancies in the control group—a protective rate of about 80 percent. The authors conclude that a multivitamin supplement containing folic acid taken from two months before conception through the end of the second month of pregnancy and taken more than five times per week can significantly reduce the risk of NTDs. (Chen, Song, et al., 2008)

## EPIDEMIOLOGIC STUDIES ON MULTIVITAMINS AND BIRTH DEFECTS

Three out of four epidemiological studies published in 1988 and 1989 showed a protective effect of multivitamin supplements with folic acid in women who took the supplement at least one month before and three months after conception (the periconceptional period). The supplement provided a 60 to 70 percent protection against NTDs. (Bower & Stanley, 1989; Mills, Rhoads, et al., 1989; Milunsky, Jick, et al., 1989; Mulinare, Cordero, et al., 1988)

In early 1993, researchers published the results of a case-control study done in Boston, Philadelphia, and Toronto. In women who used multivitamins containing folic acid for at least 28 days before and 28 days after conception, the supplement had a strong protective effect against NTDs. The authors suggest that "daily periconceptional intake of 0.4 mg of folic acid (the dose most commonly contained in over-the-counter multivitamin preparations) reduces the risk of occurrent NTDs by approximately 60 percent." (Werler, Shapiro, et al., 1993)

In a case-control study conducted by the California Birth Defects Monitoring Program, 549 mothers of infants or fetuses with neural tube birth defects were paired with 540 mothers of infants without birth defects. Using a vitamin containing folic acid in the three months *before conception* had a protective effect against NTDs. The women who used a supplement had 35 percent less risk of having babies with a neural tube defect. (Shaw, Schaffer, et al., 1995)

The epidemiologic evidence indicates that *multivitamin* use by the mother not only protects against NTDs, but may also protect against other types of birth defects, including cleft lip and cleft palate, as well as a variety of other defects. (Moyers & Bailey, 2001; Shaw, Schaffer, et al., 1995)

The prevalence of NTDs was relatively high in South Carolina, and a public health program was initiated "to prevent recurrence of NTDs among high-risk mothers with the use of folic acid during the periconceptional period." During the six years from 1992 to 1998, there was a 40 percent reduction in the incidence of neural tube defects and an increase in the use of folic acid by women during the critical months just before and after conception. The number of NTDs declined from 1.89 per 1,000 births to 0.95 per 1,000 births during this period. In 113 women who had already had one pregnancy affected by neural tube defects and who were given folic acid before and during their next pregnancy, there were no recurrences of NTDs in the subsequent pregnancy. In the general population, use of folic acid supplements increased among women of childbearing age during this period, from eight percent to more than 30 percent. These findings are "in agreement with the known protective effect of folic acid against these malformations." (Stevenson, Allen, et al., 2000)

A recent study of the rate of occurrence of NTDs in pregnancies that were conceived *after* folic acid enrichment of grain products was initiated in the U.S. suggested the possibility that mandatory fortification may be achieving a large fraction of the preventive effect that can be achieved, as it was intended to do. Previous population studies have found folic acid supplement use during the months before and after conception to be associated with a substantial decrease in the incidence of NTDs. This most recent population study found little evidence of such an association. The authors speculate that it is possible that folic acid intake in the U.S. "may have reached levels where nearly all folate-sensitive neural tube defects have been prevented." (Mosley, Cleves, et al., 2009)

Dr. Karen Bell and Dr. Godfrey Oakley of Emory University in Atlanta, Georgia, have developed a program for tracking folic acid fortification programs globally and for estimating the number of NTDs that are being prevented by such fortification. As of 2009, they indicate that 68 countries have instituted folic acid enrichment or fortification of wheat flour and/or maize flour. However, in most countries the level of fortification is not sufficient to provide most women with the recommended level of 400 mcg of folic acid daily. They conclude: "Seventeen years after folic acid was unequivocally shown to prevent spina bifida and anencephaly, we estimate that only about 10 percent of the birth defects in the world that can be prevented by folic acid are actually being prevented." (Bell & Oakley, 2009)

## COST OF 400 mcg PER DAY OF FOLIC ACID

Women can easily add 400 mcg of folic acid per day to their dietary intake by using a multivitamin containing folic acid or by consuming a breakfast cereal fortified with 400 mcg of folic acid per serving. The cost of the multivitamin supplement would be less than a dime a day, and the cost of the fortified breakfast cereal would be about 31 cents per serving without milk or 46 cents per serving with milk. All are excellent bargains, providing critically important protection from neural tube birth defects as well as overall protection of women's health. Costs cited below are based on prices in supermarkets and drug stores in the upper Midwest early in 2012.

| PRODUCT | COST PER DAY |
|---|---|
| Store-brand multivitamin/ mineral supplement | $ 0.05 |
| Brand-name multivitamin/ mineral supplement | $ 0.07 |
| Breakfast cereal fortified with 100% of the Daily Value of folic acid (cost of cereal alone, without addition of milk) | $ 0.31 |
| Breakfast cereal fortified with 100% of the Daily Value of folic acid (cost of cereal plus 1/2 cup milk) | $ 0.46 |

## Bottom Line

An abundance of data shows that women who get an extra 400 mcg of folic acid per day for one to three months prior to conception and one to three months after conception can substantially lower the risk of having a baby with a neural tube defect such as spina bifida or anencephaly. In most studies, the protective amount of folic acid was consumed in the form of a multivitamin supplement; a few studies provided folic acid as a single nutrient. For optimum protection of the fetus, it would be advisable for all women of childbearing age to consume a multivitamin containing 400 mcg of folic acid every day. Since many women do not take a multivitamin, food fortification programs have been adopted in many nations, including the U.S. These have reduced the numbers of babies born with neural tube birth defects, but not to the extent observed in women who used a supplement, so there is still an important role for multivitamins with folic acid in providing fuller protection against NTDs.

### REFERENCES


Bell, K. N., & Oakley, G. P., Jr. (2009). Update on prevention of folic acid-preventable spina bifida and anencephaly. *Birth Defects Res A Clin Mol Teratol, 85*(1), 102-107.

Berry, R. J., Li, Z., Erickson, J. D., Li, S., et al. (1999). Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med, 341*(20), 1485-1490.

Bower, C., & Stanley, F. J. (1989). Dietary folate as a risk factor for neural-tube defects: evidence from a case-control study in Western Australia. *Med J Aust, 150*(11), 613-619.

CDC. (1992). Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep, 41*(RR-14), 1-7.

CDC. (2004). Spina bifida and anencephaly before and after folic acid mandate, United States 1995-95 and 1999-2000. *MMWR, 41 (No. RR-14)*.

CDC. (2008). Use of supplements containing folic acid among women of childbearing age—United States, 2007. *MMWR, January 11, 2008, 57*(01), 5-8.

CDC. (2009). Facts About Folic Acid. www.cdc.gov/ncbddd/folicacid/

Chen, G., Song, X., Ji, Y., Zhang, L., et al. (2008). Prevention of NTDs with periconceptional multivitamin supplementation containing folic acid in China. *Birth Defects Res A Clin Mol Teratol, 82*(8), 592-596.

Czeizel, A. E., & Dudas, I. (1992). Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med, 327*(26), 1832-1835.

FDA. (1996a). Health claims and label statements; folate and neural tube defects. Final rule. (Codified in Section 101.79, Title 21, Code of Federal Regulations). *Federal Register, 61*, 8752-8781.

FDA. (1996b). Food standards: Amendment of standards of identity for enriched grain products to require addition of folic acid. *Federal Register, 61*, 8781-8797.

Gibson, T. M., Weinstein, S. J., Pfeiffer, R. M., Hollenbeck, A. R., et al. (2011). Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. *Am J Clin Nutr, 94*(4), 1053-1062.

Green, R. (2009). Is it time for vitamin B-12 fortification? What are the questions? *Am J Clin Nutr, 89*(2), 712S-716S.

Institute of Medicine. (1998). *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin and Choline.* Washington, D.C.: National Academy Press.

Mason, J. B., Cole, B. F., Baron, J. A., Kim, Y. I., et al. (2008). Folic acid fortification and cancer risk. *Lancet, 371*(9621), 1335; author reply 1335-1336.

Mills, J. L., Rhoads, G. G., Simpson, J. L., Cunningham, G. C., et al. (1989). The absence of a relation between the periconceptional use of vitamins and neural-tube defects. National Institute of Child Health and Human Development Neural Tube Defects Study Group. *N Engl J Med, 321*(7), 430-435.

Milunsky, A., Jick, H., Jick, S. S., Bruell, C. L., et al. (1989). Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. *J Am Med Assn, 262*(20), 2847-2852.

Mosley, B. S., Cleves, M. A., Siega-Riz, A. M., Shaw, G. M., et al. (2009). Neural tube defects and maternal folate intake among pregnancies conceived after folic acid fortification in the United States. *Am J Epidemiol, 169*(1), 9-17.

Moyers, S., & Bailey, L. B. (2001). Fetal malformations and folate metabolism: review of recent evidence. *Nutr Rev, 59*(7), 215-224.

MRC Vitamin Study Research Group. (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet, 338*(8760), 131-137.

Mulinare, J., Cordero, J. F., Erickson, J. D., & Berry, R. J. (1988). Periconceptional use of multivitamins and the occurrence of neural tube defects. *J Am Med Assn, 260*(21), 3141-3145.

Shaw, G. M., Schaffer, D., Velie, E. M., Morland, K., et al. (1995). Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects. *Epidemiology, 6*(3), 219-226.

Smith, A. D., Kim, Y. I., & Refsum, H. (2008). Is folic acid good for everyone? *Am J Clin Nutr, 87*(3), 517-533.

Smithells, R. W., Nevin, N. C., Seller, M. J., Sheppard, S., et al. (1983). Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet, 1*(8332), 1027-1031.

Smithells, R. W., Sheppard, S., Schorah, C. J., Seller, M. J., et al. (1980). Possible prevention of neural-tube defects by periconceptional vitamin supplementation. *Lancet, 1*(8164), 339-340.

Stevenson, R. E., Allen, W. P., Pai, G. S., Best, R., et al. (2000). Decline in prevalence of neural tube defects in a high-risk region of the United States. *Pediatrics, 106*(4), 677-683.

U.S. Preventive Services Task Force. (2009). Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med, 150*(9), 626-631.

Werler, M. M., Shapiro, S., & Mitchell, A. A. (1993). Periconceptional folic acid exposure and risk of occurrent neural tube defects. *J Am Med Assn, 269*(10), 1257-1261.

Yang, Q., Cogswell, M. E., Hamner, H. C., Carriquiry, A., et al. (2010). Folic acid source, usual intake, and folate and vitamin B-12 status in US adults: National Health and Nutrition Examination Survey (NHANES) 2003-2006. *Am J Clin Nutr, 91*(1), 64-72.