
Benefits of Folic Acid: Protection Against Neural Tube Birth Defects

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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 such as spina bifida, when taken by women of childbearing age before and during pregnancy.

In the U.S., approximately 4000 pregnancies are affected by neural tube birth defects (NTDs) each year, and worldwide these birth defects affect 300,000 or more pregnancies annually. (CDC 1997, Berry 1999) The scientific evidence makes it clear that supplementation with a multivitamin containing folic acid could prevent a large fraction of these defects.

Recommendation of the Food and Nutrition Board

In its 1998 report on new 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. (Food and Nutrition Board 1998) A number of scientific studies have shown that women who took a folic acid supplement of 360 to 800 µg per day, *in addition to their usual diet* providing 200 to 300 µg of dietary folate per day, had a reduced risk of having a baby with a neural tube defect. These 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.

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, and 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 and fortified foods and in clinical trials. It is very efficiently absorbed by the body.

Neural tube defects 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 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. (Food and Nutrition Board 1998)

Recommendation for Women Capable of Becoming Pregnant

The Food and Nutrition Board recommends “that women capable of becoming pregnant consume 400 µg 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.”

In addition to recommending that women capable of pregnancy consume supplemental folic acid from supplements or fortified foods, the Food and Nutrition Board established new Recommended Dietary Allowances (RDAs) for the amount of naturally-occurring food folate that should be consumed from the ordinary diet. For women of childbearing age, the RDAs for food folate are as shown in the table below.

<u>Group</u>	<u>RDA (dietary folate equivalents)</u>
Girls 14-18	400 micrograms per day
Adult women	400 micrograms per day
Pregnant women	600 micrograms per day

Lactating women (breast-feeding) 500 micrograms per day

One dietary folate equivalent is one microgram of naturally-occurring dietary folate, 0.5 microgram of synthetic folic acid taken on an empty stomach, or 0.6 microgram of synthetic folic acid taken with meals. It takes less of the synthetic form to be equivalent to a microgram of food folate, because the synthetic form is much better absorbed. Synthetic folic acid is the form of the nutrient used in nutritional supplements and fortified foods and the form used in clinical trials.

Key Scientific Studies

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 µg (0.36 mg) of folic acid per day. The rate of recurrence of NTDs in the supplemented group was 1 percent, compared to 5 percent in women who did not receive a supplement. The protective effect was thus an 80 percent reduction in the incidence of NTDs. (Smithells 1980 and 1983)

Smithells' study was a carefully conducted clinical trial, but it was not a randomized placebo-controlled trial, since the ethics 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.

In 1991, the Medical Research Council reported that a supplement of 4 mg (4000 µg) of folic acid had a protective effect of 72 percent against the recurrence of NTDs in 1195 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 2000 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 1000 pregnancies, compared to 23 per 1000). 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 1992)

Three out of four epidemiological studies published in 1989 also 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. (Mulinare 1988; Milunsky 1989; Bower 1989; Mills 1989)

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%." (Werler 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 1995)

The epidemiologic evidence indicates that multivitamin use by the mother not only protects against neural tube birth defects, but may also protect against other types of birth defects, including cleft lip and cleft palate (Shaw 1995), urinary tract defects (Li 1995), and defects involving the limbs (Yang 1997). A recent review by Moyers and Bailey also addresses the evidence that folate metabolism may affect a wide variety of birth defects. (Moyers and Bailey, 2001)

In addition to protecting against some birth defects, multivitamins can also play an important role in maintaining a healthier pregnancy in low income women. In a study of pregnancy outcomes in more than 400 low income women, researchers at the University of Medicine and Dentistry of New Jersey found that women who took multivitamins *with minerals* during pregnancy were less likely to suffer a preterm delivery or to have a low birth weight infant. The authors conclude that "in low income, urban women, use of prenatal multivitamin/mineral supplements may have the potential to diminish infant morbidity and mortality." (Scholl 1997)

A public health program in China was undertaken from 1993 to 1995, in which women were asked to take a supplement of 400 µg 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, with a high incidence of NTDs, there were about five neural tube defects per 1000 births among

women who did not receive the supplement. This was reduced to one per 1000 (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 1000 births for unsupplemented women. This was reduced to 0.6 per 1000 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 1999)

The prevalence of neural tube defects is 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.” As part of this education and intervention effort, a system of surveillance was initiated to provide a record of the number of pregnancies affected by NTDs. 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 1000 births to 0.95 per 1000 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 8 percent to more than 30 percent. These findings are “in agreement with the known protective effect of folic acid against these malformations.” (Stevenson 2000)

In a review of the evidence on folic acid and NTDs, a scientist from the Centers for Disease Control and Prevention concludes: “Proof for the efficacy of folic acid prophylaxis is overwhelming, and prevention efforts should not await the exact elucidation of how folic acid works, especially since babies are born every day with spina bifida and anencephaly that could have been prevented.” (Watkins 1998)

What Does the Food and Drug Administration Say?

In 1996, FDA approved 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.” Health claims for foods and supplements were authorized by Congress in the Nutrition Labeling and Education Act of 1990, and the folic acid health claim is one of only about a dozen that have been approved by FDA so far. Approval must be based on an FDA finding that the claim is supported by “significant scientific agreement.” (Food and Drug Administration 1996)

Since 1998, FDA has 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 µg per 100 grams of product), about twice the level of folate that is naturally present in whole wheat. (Food and Drug Administration 1996)

There is controversy regarding whether the level of folic acid fortification selected by FDA is sufficient to reduce the risk of NTDs in the U.S. population. The level of fortification required was initially expected to deliver an additional 80 to 100 µg of folic acid to the diets of women of childbearing age. Several studies have documented increases in blood levels of folic acid in the general population as a result of the folic acid fortification program, and one study indicates a significant reduction (almost 20 percent) in the incidence of NTDs. These are important gains, even if they do not match the impact that has been observed when women use the full recommended amount of supplemental folic acid. (Lewis 1999, Jacques 1999, Lawrence 1999, MMWR 2000, Caudill 2001, Rosenberg 2001, Choumenkovitch 2001, Honein 2001)

Dr. James Mills and Dr. Lucinda England of the National Institute of Child Health and Human Development conclude that it remains important for women of childbearing age to take a supplement with folic acid “to obtain the maximum protection against the development of NTDs.” (Mills 2001)

Are Multivitamins More Effective Than Ordinary Foods in Providing Folic Acid?

The Food and Nutrition Board of the Institute of Medicine noted that “the evidence for a protective effect from folate supplements is much stronger than that for food folate. It is certainly conceivable that, if taken in adequate quantity, food folate will be shown to be as effective as folic acid, but it remains to be demonstrated.” (Food and Nutrition Board 1998)

Researchers in Ireland compared the effectiveness of dietary guidance, food fortification, and supplement use in raising red cell folate levels in 41 women. Over a period of three months, folate levels increased significantly in the women who received supplements or fortified foods providing an additional 400 µg per day of folic acid on top of dietary levels. Women given high-folate foods or dietary advice were able to significantly increase dietary intake, but did not significantly increase red cell folate levels. The researchers concluded that “**advice to women to consume folate-rich foods as a means to optimise folate status is misleading.**” (Cuskelly 1996, emphasis added)

In a study of 189 women in the Diana Project in Minneapolis-St. Paul, researchers from the University of Minnesota studied red cell folate levels of women who consumed only natural food sources of folate, regular foods plus fortified breakfast cereals, or supplements containing folic acid. Only women using nutritional supplements achieved a protective level of red cell folate. The researchers concluded that an educational campaign and easy access to folic acid supplements are needed to ensure adequate intakes for most women. (Brown 1997)

Researchers at Boston University examined the relative effectiveness of supplementation, dietary modifications, and fortification of grain products in delivering effective amounts

of folic acid to women of childbearing age. They concluded: “Even with existing levels of food fortification, women of childbearing age should be advised to take folic acid-containing supplements on a daily basis; this will help ensure adequate folic acid intake in the large majority of women whose intake without supplementation falls below the recommended level.” (Werler 1999)

National Campaign Led by the March of Dimes and the Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) have provided leadership for the past decade in urging women of childbearing age to get 400 µg of folic acid daily, in order to help prevent neural tube birth defects. As early as 1992, CDC led the Public Health Service to adopt a public health recommendation to this effect. (CDC 1992)

In the mid-1990s, CDC and the March of Dimes jointly created and led a national campaign on folic acid to spread the message to women capable of pregnancy and to encourage physicians and other health professionals to actively recommend folic acid supplementation to women under their care. Here are the objectives as stated by the March of Dimes:

“In women who could become pregnant or who are pregnant, getting 400 µg of folic acid daily before conception and in the first few weeks of pregnancy can help prevent birth defects of the spine and brain. Consuming enough folate before pregnancy is important for these two reasons:

- An estimated 50% of all pregnancies in the United States are unplanned.
- Most women do not yet even know they are pregnant during the first few critical weeks of fetal development when the birth defects may occur.”

According to the March of Dimes, “a multivitamin containing folic acid, if taken daily, can reduce the incidence of Neural Tube Defects by up to 70 percent. However, only 18 percent of nonpregnant women aged 18-24 report taking a vitamin containing folic acid daily, and even lower percentages among women of lower income and lower education. **Approximately two thirds of women in the United States do not consume enough folic acid.**”

“The March of Dimes recommends that women of childbearing age take a multivitamin daily as part of a healthy diet rich in fortified and natural food sources. Folate is found in leafy green vegetables, whole grain foods, and citrus fruits. While a healthy and diverse diet is important, it may not be sufficient to reduce neural tube defects by 70 percent. Supplementation is essential to achieve this reduction.” (March of Dimes 2001)

The Gallup Organization recently surveyed women of childbearing age and found that, while 80 percent of the women were aware of folic acid, only about 30 percent of them were taking a supplement containing folic acid. Dr. Jennifer L. Howse, president of the

March of Dimes, called on “physicians, nurses, midwives, pharmacists, and other health professionals to use every contact they have with women of childbearing age to urge them to take a multivitamin with folic acid daily.” (March of Dimes 2002)

What Would Be the Cost of Getting 400 Micrograms Per Day of Folic Acid from a Supplement or Fortified Cereal?

Women can easily add 400 micrograms 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 µg of folic acid per serving. The cost of the supplement would be less than a dime a day, and the cost of the cereal would be about 38 cents per serving. Either is an excellent bargain, providing critically important protection from devastating neural tube birth defects as well as overall protection of women's health.

PRODUCT	COST PER DAY
Multivitamin supplement I, National brand	\$ 0.07
Multivitamin supplement II, National brand	0.09
Multivitamin supplement III, Store brand	0.05
Breakfast cereal fortified with 100 percent of the Daily Value of folic acid	0.38

Bottom Line

An abundance of data shows that women who get an extra 400 µg 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 micrograms of folic acid every day.

In addition to reducing the risk of serious birth defects, increased intakes of folic acid may have other benefits, including reducing the risk of cardiovascular disease and possibly some cancers, as discussed elsewhere in this document.

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