Title
Folic Acid Supplementation for the Prevention of Neural Tube Defects US Preventive Services Task Force Recommendation Statement

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Folic Acid Supplementation for the Prevention of Neural Tube Defects

US Preventive Services Task Force Recommendation Statement

The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF recommends that all women who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid (A recommendation) (Figure 1).

Rationale

**Importance**

Neural tube defects are major birth defects of the brain and spine that occur early in pregnancy due to improper closure of the embryonic neural tube, which may lead to a range of disabilities or death. The most common neural tube defects are anencephaly (an underdeveloped brain and an incomplete skull) and spina bifida (incomplete closing of the spinal cord).¹² Based on 2009-2011 data, the estimated average annual prevalence of anencephaly and spina bifida combined was 6.5 cases per 10,000 live births.¹³ Daily folic acid supplementation in the periconceptional period can prevent neural tube defects.¹²

Folic acid is the synthetic form of folate, a water-soluble B vitamin (B₉). Folic acid is usually given as a multivitamin, prenatal vitamin, or single supplement. It is also used to fortify cereal grain products. Folate occurs naturally in foods such as dark green leafy vegetables, legumes, and oranges.¹ However, most women do not receive the recommended daily intake of folate from diet alone.¹ National Health and Nutrition Examination Survey

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**Importance**

Neural tube defects are among the most common major congenital anomalies in the United States and may lead to a range of disabilities or death. Daily folic acid supplementation in the periconceptional period can prevent neural tube defects. However, most women do not receive the recommended daily intake of folate from diet alone.

**Objective**

To update the 2009 USPSTF recommendation on folic acid supplementation in women of childbearing age.

**Evidence Review**

In 2009, the USPSTF reviewed the effectiveness of folic acid supplementation in women of childbearing age for the prevention of neural tube defects in infants. The current review assessed new evidence on the benefits and harms of folic acid supplementation.

**Findings**

The USPSTF assessed the balance of the benefits and harms of folic acid supplementation in women of childbearing age and determined that the net benefit is substantial. Evidence is adequate that the harms to the mother or infant from folic acid supplementation taken at the usual doses are no greater than small. Therefore, the USPSTF reaffirms its 2009 recommendation.

**Conclusions and Recommendation**

The USPSTF recommends that all women who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid. (A recommendation)

NHANES) data from 2003 to 2006 suggest that 75% of non-pregnant women aged 15 to 44 years do not consume the recommended daily intake of folic acid for preventing neural tube defects. Recognition of Risk Status

Women who have a personal or family history of a pregnancy affected by a neural tube defect are at increased risk of having an affected pregnancy. However, most cases occur in the absence of any personal or family history.

Benefits of Preventive Medication

The USPSTF found convincing evidence that folic acid supplementation in the periconceptional period provides substantial benefits in reducing the risk of neural tube defects in the developing fetus. The USPSTF found inadequate evidence on how the benefits of folic acid supplementation may vary by dosage, timing relative to pregnancy, duration of therapy, or race/ethnicity.

Harms of Preventive Medication

The USPSTF found adequate evidence that the harms to the mother or infant from folic acid supplementation taken at the usual doses are no greater than small.

USPSTF Assessment

The USPSTF concludes with high certainty that the net benefit of daily folic acid supplementation to prevent neural tube defects in
Clinical Considerations

Patient Population Under Consideration
This recommendation applies to women who are planning or capable of pregnancy (Figure 2). It does not apply to women who have had a previous pregnancy affected by neural tube defects or who are at very high risk due to other factors (eg, use of certain antiseizure medications or family history). These women may be advised to take higher doses of folic acid.

Assessment of Risk
Although all women of childbearing age are at risk of having a pregnancy affected by neural tube defects and should take folic acid supplementation, some factors increase their risk, including a personal or family history of neural tube defects, use of particular antiseizure medications, maternal diabetes, obesity, and mutations in folate-related enzymes.1

Questions persist regarding increased risk of neural tube defects in some racial/ethnic groups. Birth prevalence rates are highest among Hispanic women, followed by non-Hispanic white and non-Hispanic black women.1 Genetic mutations in folate-related enzymes may vary by race/ethnicity. Dietary folate or folic acid intake differs by race/ethnicity. For example, Mexican American women may be at increased risk because of decreased consumption of fortified foods and greater intake of corn masa–based diets.1 Fewer Hispanic women (28%) report consuming 0.4 mg (400 µg) or more of folic acid daily through fortified food or supplements, compared with 39% of non-Hispanic white women.1,6

Timing
Half of all pregnancies in the United States are unplanned.6 Therefore, clinicians should advise all women who are capable of pregnancy to take daily folic acid supplements. The critical period for supplementation starts at least 1 month before conception and continues through the first 2 to 3 months of pregnancy.1,7,8

Dosage
Trials and observational studies conducted in settings without food fortification suggest that supplementation with a multivitamin containing 0.4 to 0.8 mg (400-800 µg) of folic acid decreases the risk of neural tube defects.1,7,8 Evidence shows that most women in the United States are not consuming fortified foods in a quantity needed to demonstrate optimal benefit.8 An analysis of NHANES data found that 48% of respondents of childbearing age consumed the recommended amount of folic acid from mandatorily fortified foods only.1,9

According to the National Academy of Sciences Food and Nutrition Board, the tolerable upper intake level of folic acid in women 19 years and older is 1 mg/d (1000 µg/d) from supplements...
or fortified food (excluding naturally occurring folate) and 0.8 mg/d (800 µg/d) for those aged 14 to 18 years.10 Fewer than 3% of girls and women aged 14 to 50 years receive more than 1 mg/d (1000 µg/d) of folic acid from supplements or food.3,11,12

Additional Approaches to Prevention

The Community Preventive Services Task Force recommends community-wide education campaigns to encourage women of childbearing age to take folic acid supplements.13

In 2016, the US Food and Drug Administration approved folic acid fortification of corn masa flour. This allows manufacturers to voluntarily add folic acid to corn masa flour at levels consistent with those found in other enriched cereal grains.14

Scope of Review

In 2009, the USPSTF reviewed the effectiveness of folic acid supplementation in women of childbearing age for the prevention of neural tube defects in infants.7 The current review assessed new evidence on the benefits and harms of folic acid supplementation. The USPSTF did not review the evidence on folic acid supplementation in women with a history of pregnancy affected by neural tube defects or other high-risk factors. Evidence on folic acid fortification, counseling to increase dietary intake of folic acid or naturally occurring food folate, or screening for neural tube defects is also outside the scope of this review.

Effectiveness of Preventive Medication

In 2009, the USPSTF reviewed the evidence on folic acid supplementation in women of childbearing age and found that the benefits are well-established and outweigh the harms.8

In the current review, the USPSTF evaluated 1 randomized clinical trial (RCT), 2 cohort studies, 8 case-control studies, and 2 publications from the previous USPSTF review for evidence of effectiveness of folic acid supplementation (n = at least 41 802 participants). Results were not pooled because of study heterogeneity and differences in food fortification over time.

A fair-quality RCT conducted in Hungary (1984-1992) assessed women (n = 5453) without a personal history of pregnancy affected by neural tube defects.15 Participants were randomized to receive either a daily vitamin supplement containing 0.8 mg (800 µg) of folic acid (experimental group) or a daily trace-element supplement (control group) in the periconceptional period. The trial reported no cases of neural tube defects in the experimental group and 6 cases in the control group (0% vs 0.25%; P = .01 by Fisher exact test).15 These results indicate a statistically significant lower odds of neural tube defects with folic acid supplementation (Peto odds ratio [OR], 0.13 [95% CI, 0.03-0.65]; P = .01).135

Evidence from older, fair-quality observational studies provide additional support that folic acid supplementation is beneficial.1,5 A fair-quality prospective cohort study (n = 6112) conducted in Hungary compared women who were provided a vitamin supplement containing 0.8 mg (800 µg) of folic acid before conception with unsupplemented women at the first prenatal visit (between 8 and 12 weeks of pregnancy) and showed a statistically significant effect on the odds of neural tube defects (OR, 0.11 [95% CI, 0.01-0.91]).1,16 A fair-quality retrospective cohort study conducted in the United States in women undergoing α-fetoprotein testing or amniocentesis between 15 and 20 weeks of pregnancy showed a statistically significant effect on the odds of neural tube defects among 10 713 women who took multivitamins containing folic acid in weeks 1 through 6 of pregnancy compared with 3157 women who did not take any supplements (OR, 0.27 [95% CI, 0.11-0.63]).1,17

The 8 remaining studies were fair-quality case-control studies of births occurring over 3 decades, from 1976 through 2008.8 Studies compared infants who had malformations caused by neural tube defects with either nonmalformed infants or infants who had malformations not caused by neural tube defects. Data were drawn from 2 multistate studies (National Birth Defects Prevention Study and the Slone Epidemiology Center Birth Defects Study), a 2-state study (National Institute of Child Health and

Discussion

Burden of Disease

During early fetal development, a neural tube forms that later becomes the spinal cord, brain, and neighboring protective structures (eg, spinal column), with complete closure occurring by the fourth week of pregnancy. Incomplete neural tube closure results in defects such as anencephaly and spina bifida. These defects vary in level of disability and may lead to death. Neural tube defects are among the most common major congenital anomalies in the United States.1 Based on 2009-2011 data from the Centers for Disease Control and Prevention, the estimated average annual prevalence of anencephaly and spina bifida combined was 6.5 cases per 10 000 live births.1,2

Since widespread recommendations on folic acid supplementation and the implementation of food fortification laws by the US Food and Drug Administration in 1998, prevalence rates of infants born with neural tube defects have decreased.1,2 Prevalence of neural tube defects declined from 10.7 cases per 10 000 live births before the implementation of food fortification (1995 to 1996) to 7.0 cases per 10 000 live births after fortification (1999 to 2011).2 Folic acid supplementation prevents about 1300 neural tube defects per year in the United States.1,5,15

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Other Considerations

Research Needs and Gaps

Study results on the effectiveness of folic acid supplementation in reducing neural tube defects among Hispanic women compared with white or black women have been inconsistent. Future research should continue to evaluate differences in diverse populations.1

Clinical Review & Education

US Preventive Services Task Force

USPSTF Recommendation: Folic Acid to Prevent Neural Tube Defects

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Human Development Neural Tube Defects Study), and 2 single- 
state studies (Texas Neural Tube Defect Project and the California 
Birth Defects Monitoring Program).1 Older case-control studies 
conducted before implementation of food fortification laws were 
generally consistent with the more recent evidence showing that 
folate acid supplementation is beneficial for the prevention of neural 
tube defects (OR range, 0.6-0.7 [in 3 of 4 studies]). Newer case- 
control studies conducted after food fortification did not show a 
protective effect of folic acid supplementation on neural tube 
defects (OR range, 0.93-1.40 [95% CI included the null]).1

Ethical considerations limited the use of RCT methods to 
study the effects of folic acid supplementation after food fortifi- 
cation. The newer studies are more subject to design issues than 
the older ones, which had fewer design flaws.1 Case-control stud- 
ies have the potential for selection and recall bias, both of which 
can reduce the observed effect of folic acid supplementation on 
nervous tube defects. Another issue with all study designs is the 
relative rarity of the outcome and the challenge of adequately 
powering studies to determine benefits. Another potential expla- 
nation for the findings is that the majority of cases of neural tube 
defects due to folate deficiency have now been prevented, and 
subsequent cases result from a different etiology. Despite this 
possible rationale, evidence indicates that most women are not 
consuming fortified foods at the level needed for optimal benefit. 
Inadequate folate intake continues to leave nearly one-fourth of 
the US population with suboptimal red blood cell folate 
concentration.1-19

Three fair-quality case-control studies (n = 11 154) examined 
the effects of folic acid supplementation by race/ethnicity.1,18-20 
One study found that folic acid supplementation may be less pro- 
tective among Hispanic women compared with white or black 
women.18 A second study found a statistically nonsignificant 
increased risk of neural tube defects with supplementation among 
Hispanic women (OR adjusted for consistent users vs nonusers, 
2.20 [95% CI, 0.98-4.92]).19 A third study found that periconcept- 
tional supplementation did not decrease the risk of neural tube 
defects and reported no differences in effect by race/ethnicity.20 
These inconsistent results among Hispanic women could be a 
result of chance due to small sample sizes.

Eight fair-quality case-control studies addressed dose, timing, 
or duration of therapy.1 Of these 8 studies, 4 (n = 26 791) provided 
information on dose, 5 (n = 26 808) provided information on tim- 
ing, and none provided information on duration. Across the stud- 
ies, evidence was inconsistent that the benefits of folic acid supple- 
mentation differ by dosage or timing.1

Potential Harms of Preventive Medication

The USPSTF found adequate evidence that folic acid supplementa-
tion does not have serious harms. One fair-quality trial and 1 fair-
quality cohort study did not find evidence of a statistically signifi-
cant increased risk of pregnancy with twins in women.1

In the Hungarian trial (n = 5 453), the rate of twin pregnancy was 
not statistically significantly different between the multivitamin and 
trace-element groups (OR, 1.4 [95% CI, 0.89-2.21]).1,21 In a retro-
spective, population-based cohort study in Norway (n = 176 042), 
no association was found between folic acid supplementation and 
twin pregnancy (OR, 1.04 [95% CI, 0.91-1.18]) after adjusting for use 
of in vitro fertilization, maternal age, and parity.22

The Hungarian trial examined adverse events in women and 
found a potential increased risk of maternal weight gain, diarrhea, 
and constipation at 12 weeks of pregnancy. However, there was a 
low event rate, and these symptoms could have occurred by 
chance. These symptoms are also associated with pregnancy.1,15

Three systematic reviews of observational studies (n = at 
least 14 438 participants) evaluated childhood asthma, wheezing, 
or allergies and found inconsistent evidence of harms,1,12,13-24 
Evidence was also inconsistent on the harms of folic acid supple- 
munication differing by dosage and timing. No evidence was found 
on harms differing by duration of therapy.1

Other potential hypothesized harms of folic acid supple-
micit include the masking of symptoms of vitamin B12 
deficiency and subsequent neurologic complications, carcino-
genic effects, asthma/allergic reactions, and interactions with 
medications.1,7,10 The USPSTF found no significant evidence of 
these potential harms.

Estimate of Magnitude of Net Benefit

The USPSTF found no new substantial evidence on the benefits 
and harms of folic acid supplementation that would lead to a 
change in its recommendation from 2009.7 The USPSTF assessed 
the balance of the benefits and harms of folic acid supplementation 
in women of childbearing age and determined that the net 
benefit is substantial. Evidence is adequate that the harms to the 
mother or infant from folic acid supplementation taken at the 
usual doses are no greater than small. Therefore, the USPSTF 
reaffirms its 2009 recommendation that all women who are plan- 
ning or capable of pregnancy take a daily supplement containing 
0.4 to 0.8 mg (400-800 μg) of folic acid.8

How Does Evidence Fit With Biological Understanding?

Genetic predisposition and environmental influences are thought 
to contribute to neural tube defects. These environmental influ-
ences are being investigated. An important environmental influ- 
ence is the consumption of folate. The mechanism of action of 
folate in the prevention of neural tube defects is unknown. Folate 
acts as a coenzyme in the synthesis of nucleic acids and the 
metabolism of amino acids. An important function of folate is its 
role in single-carbon transfers, which are important in methylation 
reactions and in purine and pyrimidine synthesis. Folate is neces-
sary for the regulation of DNA synthesis and function; reduced 
concentrations of folate may limit the number of methyl groups avail-
able for DNA replication and methylation.1,7,10

Evidence suggests that mutation in the MTHFR gene, which en- 
codes the enzyme methenyltetrahydrofolate reductase, is a risk 
factor for neural tube defects. This enzyme regulates folate and ho-
mocysteine levels. Persons who have this gene mutation have 
decreased folate levels, which reduces the conversion of homocys-
teine to methionine and may increase the risk of neural tube 
defects.1,25 Folic acid consumption may help diminish the effects of 
the gene mutation.

Response to Public Comment

A draft version of this recommendation statement was posted for 
public comment on the USPSTF website from May 10 to June 6, 
2016. Some comments requested a more detailed definition of 
“excessive” folic acid. In response, the USPSTF added information
about tolerable upper intake levels for folic acid. Other comments suggested emphasizing that many women do not meet daily recommended amounts of folic acid and adding language on the potential harms of folic acid supplementation. The USPSTF added language about the harms of supplementation and the difficulty of consuming enough folic acid from food alone.

**Update of Previous USPSTF Recommendation**

This recommendation reaffirms the 2009 recommendation statement on folic acid supplementation in women of childbearing age. The current statement recommends that all women who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 μg) of folic acid.

**ARTICLE INFORMATION**

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Author Contributions: Dr Bibbins-Domingo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The USPSTF members contributed equally to the recommendation statement.

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**REFERENCES**


**Recommendations of Others**

The Health and Medicine Division of the National Academies (formerly the Institute of Medicine), American College of Obstetricians and Gynecologists, American Academy of Family Physicians, US Public Health Service, Centers for Disease Control and Prevention, American Academy of Pediatrics, American Academy of Neurology, and American College of Medical Genetics and Genomics recommend that women who are capable of becoming pregnant should take at least 0.4 mg (400 μg) of folic acid daily.2,10,26-30 The American College of Obstetricians and Gynecologists, Centers for Disease Control and Prevention, and several other organizations recommend that women with a history of neural tube defects or other high-risk factors take 4 mg (4000 μg) of folic acid daily.31-33


