

Folic Acid Supplementation to Prevent Neural Tube Defects

US Preventive Services Task Force

Reaffirmation Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Neural tube defects are among the most common congenital malformations in the US, with an estimated 3000 pregnancies affected each year. Many of these neural tube defects are caused by low folate levels in the body.

OBJECTIVE The US Preventive Services Task Force (USPSTF) commissioned a reaffirmation evidence update on the benefits and harms of folic acid supplementation.

POPULATION Persons who are planning to or could become pregnant.

EVIDENCE ASSESSMENT The USPSTF concludes that, for persons who are planning to or could become pregnant, there is high certainty that folic acid supplementation has a substantial net benefit to prevent neural tube defects in their offspring.

RECOMMENDATION The USPSTF recommends that all persons planning to or who could become pregnant take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid. (A recommendation)

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Summary of Recommendation

Population	Recommendation	Grade
Persons who plan to or could become pregnant	The USPSTF recommends that all persons planning to or who could become pregnant take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid.	A

USPSTF indicates US Preventive Services Task Force.

See the Summary of Recommendation figure.

Pathway to Benefit

To achieve benefit, persons planning to or who could become pregnant should start daily folic acid supplementation at least 1 month prior to anticipated conception and continue through the first 2 to 3 months of pregnancy.

Preamble

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 to improve the health of people nationwide.

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.

The USPSTF is committed to mitigating the health inequities that prevent many people from fully benefiting from preventive services. Systemic or structural racism results in policies and practices, including health care delivery, that can lead to inequities in health.

The USPSTF recognizes that race, ethnicity, and gender are all social rather than biological constructs. However, they are also often important predictors of health risk. The USPSTF is committed to helping reverse the negative impacts of systemic and structural racism, gender-based discrimination, bias, and other sources of health inequities, and their effects on health, throughout its work.

Importance

Neural tube defects are among the most common congenital malformations in the US, with an estimated 3000 pregnancies affected each year.¹ Many of these neural tube defects are caused by low folate levels in the body of the pregnant person. The Centers for Disease Control and Prevention estimated that spina bifida occurs in 3.9 of 10 000 live births in the US, anencephaly in 2.5 of 10 000 live births, and encephalocele in 1 of 10 000 live births.² Neural tube defects can result in death and a range of disabilities affecting children. Children with encephaloceles have an increased mortality rate, with many survivors having neurologic and developmental deficits.³⁻⁵ Common disabilities from spina bifida include lower limb weakness and paralysis, sensory loss, bowel and bladder dysfunction, orthopedic abnormalities (eg, clubfoot, contractures, hip dislocation, scoliosis, or kyphosis), and ventriculomegaly (which may require placement of ventricular-peritoneal shunts).⁶⁻⁸ Anencephaly is life-limiting in early infancy.⁹

Folate refers to vitamin B₉, a water-soluble B vitamin that occurs in many chemical forms, including naturally in foods such as leafy greens, fruits, nuts, beans, peas, seafood, eggs, dairy products, meat, and poultry.¹⁰ Folic acid is the term applied to the synthetic form of folate that is found in supplements and added to fortified foods. Folic acid supplementation for persons in the periconceptional period has been found to reduce the risk of neural tube defects in offspring.^{11,12} Despite folic acid fortification of food and supplementation guidelines, folic acid deficiency remains a concern in the US. Low levels of maternal folate may be due to inadequate dietary intake, poor intestinal absorption, medication use that interferes with folic acid function, and impaired folate metabolism.¹⁰ Survey data from 1998 to 2016 found that approximately 20% to 40% of women who were recently pregnant or trying to get pregnant reported taking periconceptional folic acid supplements, and those with an unintended pregnancy were 4 to 5 times less likely to have taken periconceptional folic acid supplements.¹⁰

USPSTF Assessment of Magnitude of Net Benefit

In 2017, the USPSTF reviewed the evidence for folic acid supplementation and issued an A recommendation.¹² The USPSTF has decided to use a reaffirmation deliberation process to update this recommendation. The USPSTF uses the reaffirmation process for well-established, evidence-based current standards of practice in primary care for which only a very high level of evidence would justify a change in the grade of the recommendation. In its deliberation of the evidence, the USPSTF considers whether the new evidence is of sufficient strength and quality to change its previous conclusions about the evidence.

Using a reaffirmation process, the USPSTF concludes that, for persons who are planning to or could become pregnant, there is high certainty that folic acid supplementation has a **substantial net benefit**.

See the **Table** for more information on the USPSTF recommendation rationale and assessment and the **eFigure** in the Supplement for information on the recommendation grade. See the **Figure** for a summary of the recommendation for clinicians. For more details on the methods the USPSTF uses to determine net benefit, see the USPSTF Procedure Manual.¹³

Practice Considerations

Patient Population Under Consideration

This recommendation applies to persons who are planning to or could become pregnant. It does not apply to persons who have had a previous pregnancy affected by neural tube defects or who are at very high risk because of other factors (eg, use of certain antiseizure medications or family history). It does not apply to persons taking certain medications known to block the function of folic acid (eg, methotrexate, carbamazepine, and valproic acid).

Definitions

Neural tube defects are caused by a failure of closure of the embryonic neural tube, which results in birth defects of the brain, spinal cord, and overlying tissues. The most common forms of neural tube defects are anencephaly, encephalocele, and spina bifida.¹⁴ Anencephaly occurs when the cranial portion of the neural tube fails to close. Affected infants are born without portions of the brain and skull. Anencephaly is life-limiting in early infancy. Encephalocele occurs when cranial defects allow portions of the brain and meninges to protrude. Spina bifida is a group of conditions that vary in severity and include myelomeningocele (protrusion of the spinal cord and meninges through a spinal defect), meningocele (protrusion of meninges through a spinal defect), and spina bifida occulta (spinal defect without any protrusion).¹⁰

Assessment of Risk

All pregnancies are at risk for neural tube defects, and persons who are planning to or could become pregnant should take folic acid supplements. Certain risk factors convey a higher risk, and individuals with these risk factors should talk to their health care professional. These factors include personal, partner, or family history of neural tube defects, malabsorption caused by bariatric procedures, the use of certain antiseizure medicines, and genetic mutations in folate-related enzymes.¹⁵⁻¹⁹ Pregestational diabetes and obesity have been associated with an increased risk of neural tube defects.^{20,21} Ethnic groups such as First Nation persons in Canada and Hispanic persons in California are thought to be at higher risk of neural tube defects.^{22,23} It is unclear, however, whether this is related to a higher risk of genetic variations among these groups or due to differential intake of folic acid-fortified foods.¹⁰

Timing

The neural plate completes its formation and closure early in pregnancy (usually 26 to 28 days after fertilization).¹⁷ This means the

Table. Summary of USPSTF Rationale

Rationale	Assessment
Benefits of intervention and treatment	The USPSTF found convincing evidence that supplements containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid taken in the periconceptual period reduce the risk for neural tube defects.
Harms of early detection and intervention and treatment	The USPSTF found adequate evidence that folic acid supplementation at usual doses is not associated with serious harms.
USPSTF assessment	Using a reaffirmation deliberation process, the USPSTF concludes with high certainty that for persons who are planning to or who could become pregnant, the net benefit of folic acid supplementation is substantial.

Abbreviation: USPSTF, US Preventive Services Task Force.

critical period for folic acid supplementation starts at least 1 month before conception and continues through the first 2 to 3 months of pregnancy. Nearly half of all pregnancies in the US are unplanned; to gain the full benefits of supplementation, clinicians should advise all persons who plan to or who could become pregnant to take daily folic acid.²⁴

Dosage

Good evidence from studies in settings without fortification of food suggests that an over-the-counter multivitamin with between 0.4 mg (400 µg) (the generally available dose) and 0.8 mg (800 µg) of folic acid daily reduces the risk for neural tube defects.^{10,12} Clinical practice guidelines from professional medical and public health organizations recommend a minimum folic acid supplemental daily intake of 400 µg for all persons who are planning a pregnancy or could become pregnant.²⁵⁻²⁸

Since 1998, specific enriched cereal grain products in the US have been fortified with folic acid. In 2016, the US Food and Drug Administration began allowing corn masa flour to be voluntarily fortified with folic acid.¹⁰ Evidence shows that persons who may become pregnant are not consuming fortified foods at a quantity to provide optimal benefit for prevention of neural tube defects.^{12,29} Therefore, all persons planning to or who could become pregnant should take a daily supplement of at least 400 µg.

Additional Tools and Resources

The Community Preventive Services Task Force recommends community-wide education campaigns to promote the use of folic acid supplements among persons of childbearing age (<https://www.thecommunityguide.org/findings/pregnancy-health-community-wide-campaigns-promote-use-folic-acid-supplements.html>).

Reaffirmation of Previous USPSTF Recommendation

This recommendation is a reaffirmation of the USPSTF 2017 recommendation statement. In 2017, the USPSTF reviewed the evidence for folic acid supplementation to prevent neural tube defects and found convincing evidence that the benefits of supplementation substantially outweighed the harms (A recommendation).¹² In the current update, the USPSTF found no new substantial evidence that could change its recommendation and, therefore, reaffirms its recommendation that all persons planning to or who could become pregnant take a daily supplement of folic acid.

Supporting Evidence

Scope of Review

To reaffirm its recommendation, the USPSTF commissioned a reaffirmation evidence update.^{10,30} The aim of evidence updates that support the reaffirmation process is to identify new and substantial evidence sufficient to change the prior recommendation.¹³ The reaffirmation update focuses on targeted key questions on the benefits and harms of folic acid supplementation.

Benefits of Folic Acid Supplementation

In 2017, the USPSTF reviewed the evidence on the benefits of folic acid supplementation to prevent neural tube defects and found convincing evidence that the benefits of supplementation were significant. Three fair-quality observational studies (reported in 4 publications) published since the last USPSTF recommendation reported on the association between folic acid supplementation and neural tube defects (n = 990 372).^{10,30} Two cohort studies were in populations without food fortification (Norway and Japan) and the third was a case-control study set in the US and Canada prior to and after the introduction of food fortification.^{10,30} The Norwegian cohort study (n = 896 674 live births and stillborn infants) reported results by time periods (1999-2005, 2006-2013, and overall, 1999-2013).^{31,32} In Norway, folic acid supplementation was first recommended in 1999 and folic acid was not included in most multivitamins until 2004. The authors hypothesized that the study periods corresponded to lesser (1999-2005) and greater (2006-2013) adherence to recommendations regarding folic acid supplementation. The study reported a statistically significant reduction in neural tube defects in women taking folic acid supplementation in the period corresponding to greater adherence (2006 to 2013) but not in other periods. The Japanese cohort (n = 92 269) compared adequate users of folic acid supplements (started before conception) with inadequate users (started after pregnancy recognition or nonuse of folic acid supplements). Neural tube defect outcomes included spina bifida, anencephaly, and encephalocele. The study reported no statistically significant differences associated with folic acid supplementation.³³ Both cohort studies drew from general populations. The case-control study set in the US and Canada in the period following food fortification focused on high-risk participants. A subgroup of participants (123 cases and 1306 controls) with pregestational diabetes and prepregnancy obesity was included in the review. This study reported no statistically significant associations between daily or less than daily folic acid

Figure. Clinician Summary: Folic Acid Supplementation for the Prevention of Neural Tube Defects

What does the USPSTF recommend?	<p>Persons who plan to or could become pregnant: Take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid. Grade: A</p>
To whom does this recommendation apply?	This recommendation applies to all persons who are planning to or could become pregnant. It does not apply to persons who have had a previous pregnancy affected by neural tube defects or who are at very high risk due to other factors such as family history or those taking medication known to block the function of folic acid.
What's new?	This recommendation is consistent with the 2017 USPSTF recommendation.
How to implement this recommendation?	All persons who are planning to or could become pregnant should take a daily supplement or multivitamin containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid.
How often?	<ul style="list-style-type: none"> Supplementation should be taken daily. The critical period for folic acid supplementation starts at least 1 month before conception and continues through the first 2 to 3 months of pregnancy. Nearly half of all pregnancies in the US are unplanned, meaning that many persons may not know they are pregnant during the crucial time. To gain the full benefits of supplementation, clinicians should advise all persons who plan to or who could become pregnant to take a daily folic acid supplement.
Why is this recommendation and topic important?	<ul style="list-style-type: none"> Neural tube defects are caused by a failure of closure of the embryonic neural tube, which results in birth defects of the brain, spinal cord, and overlying tissues. The most common forms of neural tube defects are anencephaly, encephalocele, and spina bifida. Neural tube defects are among the most common congenital malformations in the US, with an estimated 3000 pregnancies affected each year. Neural tube defects can result in death and a range of disabilities affecting children. Daily supplementation with folic acid is shown to prevent neural tube defects.
What are additional tools and resources?	The Community Preventive Services Task Force recommends community-wide education campaigns to promote the use of folic acid supplements among persons of childbearing age (https://www.thecommunityguide.org/findings/pregnancy-health-community-wide-campaigns-promote-use-folic-acid-supplements.html).
Where to read the full recommendation statement?	Visit the USPSTF website (https://www.uspreventiveservicestaskforce.org/uspstf/) or the JAMA website (https://jamanetwork.com/collections/44068/united-states-preventive-services-task-force) to read the full recommendation statement. This includes more details on the rationale of the recommendation, including benefits and harms; supporting evidence; and recommendations of others.

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.

USPSTF indicates US Preventive Services Task Force.

supplementation, compared with no supplementation, and neural tube defects.³⁴

The USPSTF also reviewed data on whether the benefits of folic acid supplementation differ by timing. In the previously mentioned Norwegian study, there was no effect of folic acid supplementation regardless of the timing of folic acid supplementation in the period corresponding to lesser adherence (1999-2005) and in the overall period (1999-2013). In the second period (2006-2013), the results demonstrated a benefit of folic acid supplementation regardless of timing (before pregnancy only: adjusted relative risk [aRR], 0.54 [95% CI, 0.31-0.91]; before and during pregnancy: aRR, 0.49 [95% CI, 0.29-0.83]; and during pregnancy only: aRR, 0.62 [95% CI, 0.39-0.97]).^{10,30}

Harms of Folic Acid Supplementation

In 2017, the USPSTF reviewed the evidence on the harms of folic acid supplementation to prevent neural tube defects and found adequate evidence that folic acid supplementation at usual doses is not associated with serious harms. Six fair-quality cohort studies and 1 fair-quality case-control study published since the 2017 USPSTF recommendation examined the potential association between folic acid supplementation and autism spectrum disorder (ASD) (n = 761 125).^{10,30} No study reported statistically significant associations between supplementation and increased risk of ASD.

Two studies reported statistically significant reductions of autism associated with folic acid supplementation. Other studies in similar geographic settings or populations that used different measures of exposure or comparators reported no association between folic acid supplementation and autism. Three studies reported on associations between folic acid supplementation and ASD by dose and found no differences. Two studies reported on associations between folic acid supplementation and ASD by timing. Neither reported harms; however, 1 study reported a statistically significant reduction of ASD associated with folic acid supplementation initiation in weeks 5 to 8 of the pregnancy.^{10,30}

One high-quality trial reported on the differences in twin deliveries based on the dose of folic acid. It found no differences between an exposure of 4 mg vs 0.4 mg of folic acid daily. No studies reported on the overall risk, timing, or duration of twin gestations and folic acid supplementation.^{10,30} One cohort study (n = 429 004) found no association between folic acid supplementation and maternal cancer.^{10,30}

How Does Evidence Fit With Biological Understanding?

Adequate maternal folate levels are important in preventing neural tube defects; however, the mechanism by which folate reduces this risk is not well understood. Folate is necessary for nucleotide synthesis and DNA and RNA function.¹⁰ Inadequate folate levels im-

pair nucleotide synthesis and DNA and RNA replication, and may lead to incomplete neural folds and subsequent neural tube defects.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from February 21, 2023, to March 20, 2023. Most comments agreed with the conclusions of the USPSTF. Commenters requested additional information on the dosage of folic acid. The USPSTF wishes to clarify that the generally available dosage for folic acid supplementation is between 0.4 and 0.8 mg daily. The most common dosages from the included studies were in this range. Women at higher risk of neural tube defects may require dosages above this range and should speak with their clinician about this. Based on comments, the USPSTF also included information on naturally occurring sources of folate.

Research Needs and Gaps

Studies are needed that provide more information on the following.

- More research is needed to better understand how genetic variants such as *MTHFR* slow folate metabolism and how these variants affect strategies for folic acid supplementation.
- More research is needed on the effectiveness of folic acid supplementation in reducing neural tube defects among those disproportionately affected by the condition, including Hispanic persons.
- More research is needed on factors that contribute to variations in adherence to supplementation.

Recommendations of Others

The American College of Obstetricians and Gynecologists, American Academy of Family Physicians, and American Academy of Pediatrics all recommend folic acid supplementation of 400 µg (0.4 mg) per day for persons of reproductive age who are planning to become pregnant and are at average risk of neural tube defects (ie, without a prior pregnancy with a neural tube defect).²⁵⁻²⁷

ARTICLE INFORMATION

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