

# AMERICAN ACADEMY OF PEDIATRICS

Committee on Genetics

## Folic Acid for the Prevention of Neural Tube Defects

**ABSTRACT.** The American Academy of Pediatrics endorses the US Public Health Service (USPHS) recommendation that all women capable of becoming pregnant consume 400  $\mu\text{g}$  of folic acid daily to prevent neural tube defects (NTDs). Studies have demonstrated that periconceptional folic acid supplementation can prevent 50% or more of NTDs such as spina bifida and anencephaly. For women who have previously had an NTD-affected pregnancy, the Centers for Disease Control and Prevention (CDC) recommends increasing the intake of folic acid to 4000  $\mu\text{g}$  per day beginning at least 1 month before conception and continuing through the first trimester. Implementation of these recommendations is essential for the primary prevention of these serious and disabling birth defects. Because fewer than 1 in 3 women consume the amount of folic acid recommended by the USPHS, the Academy notes that the prevention of NTDs depends on an urgent and effective campaign to close this prevention gap.

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ABBREVIATIONS. NTDs, neural tube defects; USPHS, US Public Health Service; CDC, Centers for Disease Control and Prevention; MRC, Medical Research Council; IOM, Institute of Medicine; AAP, American Academy of Pediatrics.

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### BACKGROUND

Neural tube defects (NTDs) are among the most common birth defects contributing to infant mortality and serious disability. NTDs, which include anencephaly, spina bifida, and encephalocele, occur in approximately 1 of 1000 births in the United States.<sup>1</sup> An estimated 4000 pregnancies are affected with NTDs each year. More than one third of these pregnancies are spontaneously lost or electively terminated; thus, about 2500 infants per year are born with an NTD. The results of 2 randomized controlled trials and several observational studies showed that 50% or more of NTDs can be prevented if women consume a folic acid-containing supplement before and during the early weeks of pregnancy<sup>2,3</sup> in addition to the folate in their diet. Based on a synthesis of these data, the US Public Health Service (USPHS) and Centers for Disease Control and Prevention (CDC) recommendations were developed.<sup>4,5</sup> Because the evidence for folic acid prevention evolved over time, there are two separate recommendations: one for women who have no history of a previous NTD-affected pregnancy and one

for women who have had a previous NTD-affected pregnancy.

### WOMEN WITH NO HISTORY OF A PREVIOUS NTD-AFFECTED PREGNANCY

Of children with an NTD, 95% are born to couples with no family history of these defects. Evidence to date suggests that supplementation with a multivitamin containing 400 (0.4 mg)  $\mu\text{g}$  of folic acid prevents the occurrence of >50% of NTDs when it is taken before conception and continued throughout the first trimester of pregnancy.<sup>5</sup> The USPHS recommends that all women of childbearing age who are capable of becoming pregnant take 400  $\mu\text{g}$  of folic acid daily.<sup>5</sup> Implementing this recommendation may provide the opportunity for primary prevention of 50% or more of these serious disabling birth defects. Regular and ongoing ingestion of folic acid by women of childbearing age is necessary because approximately half of the pregnancies in the United States are unplanned,<sup>6</sup> and neural tube closure occurs during the first 4 weeks of gestation.<sup>7</sup> Despite the publication of the USPHS recommendation in September 1992, a 1998 poll showed that 70% of women aged 18 to 45 years still are not following the USPHS recommendation.<sup>8</sup>

### WOMEN WHO HAVE HAD A PREVIOUS NTD-AFFECTED PREGNANCY

Among US couples who have had a child with an NTD, the recurrence risk is 2% to 3% in subsequent pregnancies.<sup>9</sup> In 1991, the Medical Research Council (MRC) Vitamin Study Group reported the results of a well-designed, prospective, randomized trial of folic acid supplementation for the prevention of NTDs in pregnancies of women who had a previous child with an NTD, and the CDC published its recommendations for consumption of 4000 (4 mg)  $\mu\text{g}$  of folic acid.<sup>4</sup> The results of the MRC study conclusively demonstrated that a daily dosage of 4000  $\mu\text{g}$  of folic acid, in addition to folate in the diet, before and during early pregnancy resulted in a 71% reduction of recurrence of NTDs. The addition of other vitamins to the dosage of folic acid did not reduce the risk further. Use of multivitamins without folic acid did not result in a reduced risk for NTDs. The MRC study did not explore the possible benefit of a dosage lower than 4000  $\mu\text{g}$  of folic acid. However, an earlier nonrandomized study conducted in the United Kingdom suggested that a lower dosage, 360  $\mu\text{g}$  daily, resulted in a comparable reduction of recurrence of NTDs.<sup>10</sup> Although adverse maternal or fetal effects of a daily 4000  $\mu\text{g}$  dosage of folic acid were

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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not detected by the MRC study, the small size of the study groups precluded detection of uncommon adverse effects.

#### FOLATE AND FOLIC ACID

*Folic acid*, also known as pteroylmonoglutamic acid, is a synthetic compound used in dietary supplements and fortified foods. The term *folate* includes all compounds that have the vitamin properties of folic acid—including folic acid and naturally occurring compounds in food.<sup>11</sup> The average diet in the United States contains 200  $\mu\text{g}$  of naturally occurring food folate, which is less bioavailable than folic acid.<sup>12</sup> Additional intake of foods rich in folate could raise the average intake, but it has not been demonstrated that increased consumption of food folate would prevent NTDs as effectively as a daily vitamin supplement containing 400  $\mu\text{g}$  of folic acid. A small comparison study suggests that blood folate concentrations are increased much more by folic acid supplementation than by naturally occurring food folate in the diet.<sup>13</sup> Economic and social circumstances may make an adequate increase in dietary folate difficult or unlikely, and the behavioral change required among a large fraction of women may take years to achieve.

Folic acid is a water-soluble vitamin that has no known toxicity. However, higher doses of folic acid can correct the anemia of vitamin B<sub>12</sub> deficiency (pernicious anemia), which might be an important clue to the presence of vitamin B<sub>12</sub> deficiency in some instances. Folic acid does not prevent the neurologic consequences of vitamin B<sub>12</sub> deficiency, and, for this reason, the USPHS recommendation cautioned that intake of folate should be not >1000  $\mu\text{g}$  per day. However, the Institute of Medicine (IOM) Food and Nutrition Board recently set the tolerable upper intake limit of synthetic folic acid at 1000  $\mu\text{g}$ , thus eliminating food folate from the calculation.<sup>14</sup> Because pernicious anemia rarely occurs before the age of 50 years, it is likely to be rare among women consuming folic acid during the reproductive years. Folic acid has been consumed by about a quarter of all women for many years and extensively during later pregnancy without apparent adverse effects; however, studies that definitively address the question of maternal and fetal safety of folic acid are not available.

The IOM Food and Nutrition Board's recommended dietary allowance (RDA) for folate is 400  $\mu\text{g}$  for adults and 600  $\mu\text{g}$  for pregnant women.<sup>14</sup> To reduce the risk for NTDs, the IOM recommended that women capable of becoming pregnant consume 400  $\mu\text{g}$  of folic acid daily from fortified foods, vitamin supplements, or a combination of the two. This is in addition to the naturally occurring folate obtained from a varied diet.<sup>14</sup> The majority of multivitamin preparations contain 400  $\mu\text{g}$  of folic acid. These preparations are available over the counter and are already being taken by about 30% of non-pregnant women aged 18 to 45 years in the United States.<sup>8</sup> Tablets containing folic acid alone are available over the counter in dosages up to 800  $\mu\text{g}$  but the availability is very limited when compared with

multivitamin preparations. Folic acid tablets in a 1000  $\mu\text{g}$  dose are available by prescription only. This preparation is most frequently utilized by women who are taking 4000  $\mu\text{g}$  because of a previous NTD-affected pregnancy.

In March 1996, the Food and Drug Administration mandated that enriched cereal-grain products be fortified with 140  $\mu\text{g}$  of folic acid per 100 g of flour.<sup>15</sup> This measure increases the proportion of women who consume the USPHS-recommended daily dosage of 400  $\mu\text{g}$  of folic acid only an additional 3%, because this fortification level will provide the average woman only an additional 100  $\mu\text{g}$  of folic acid per day (unpublished data, 1992).

#### RECOMMENDATIONS

1. ***Prevention for Women With No History of a Previous NTD-Affected Pregnancy.*** The American Academy of Pediatrics (AAP) endorses the USPHS recommendation that all women of child-bearing age who are capable of becoming pregnant should consume 400 (0.4 mg)  $\mu\text{g}$  of folic acid daily. Because of the high rate of unplanned pregnancies in the United States, the AAP encourages efforts at devising a program of food fortification to provide all women a daily intake of 400  $\mu\text{g}$  of folic acid. In the absence of optimal fortification, the AAP encourages women to consume 400  $\mu\text{g}$  of folic acid daily in addition to eating a healthy diet. At present, the most convenient, inexpensive, and direct way to meet the recommended dosage is by taking a multivitamin containing 400  $\mu\text{g}$  of folic acid, but efforts to increase the availability of folic acid-only supplements should be encouraged for women who prefer not to take multivitamins. Because the risk for NTDs is not totally eliminated by folic acid use, routine prenatal screening for NTDs is still advisable.
2. ***Prevention for Women Who Have Had a Previous NTD-Affected Pregnancy.*** Women with a history of a previous pregnancy resulting in a fetus with an NTD should be advised of the results of the MRC study. During times in which a pregnancy is not planned, these high-risk women should consume 4000 (4 mg)  $\mu\text{g}$  of folic acid per day. However, they should be offered treatment with 4000  $\mu\text{g}$  of folic acid per day starting 1 month before the time they plan to become pregnant and throughout the first 3 months of pregnancy, unless contraindicated. Women should be advised not to attempt to achieve the 4000  $\mu\text{g}$  daily dosage of folic acid by taking over-the-counter or prescription multivitamins containing folic acid because of the possibility of ingesting harmful levels of other vitamins, for example, Vitamin A.<sup>17</sup> It should be noted that 4000  $\mu\text{g}$  of folic acid did not prevent all NTDs in the MRC study. Therefore, high-risk patients should be cautioned that folic acid supplementation does not preclude the need for counseling or consideration of prenatal testing for NTDs.
3. ***Prevention for Other High-Risk Persons.*** No intervention or observational studies address prevention for other high-risk persons. Women with a close

relative (eg, sibling, niece, or nephew) who has an NTD (risk is approximately 0.3% to 1.0%), women with type 1 diabetes mellitus (risk is approximately 1%), women with seizure disorders being treated with valproic acid or carbamazepine (risk is approximately 1%), and women or their partners who have an NTD (risk may be 2% to 3%)<sup>18</sup> and are planning a pregnancy should discuss with their physician the risk for an affected child and the advantages and disadvantages of increasing their daily periconceptional folic acid intake to 4000 µg.

4. **Public Health Programs: Supplementation, Surveillance, and Food Fortification.** The AAP recommends that the Department of Health and Human Services expeditiously devise and implement an educational program to prevent folic acid-preventable NTDs throughout the use of supplements, fortified foods, or a combination of both. The program should support surveillance of effectiveness and adverse outcomes to further refine the effective folate dose and mechanisms of actions. In light of the recent IOM recommendation, the AAP also encourages additional efforts at devising a program of food fortification with folic acid to provide all women capable of becoming pregnant a daily intake of 400 µg of folic acid.

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REFERENCES

- Centers for Disease Control and Prevention. Surveillance for anencephaly and spina bifida and the impact of prenatal diagnosis. United States, 1985–1994. *MMWR*. 1996;44(SS-4):1–13
- MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991; 338:131–137
- Czeizel AE, Dudás I. Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. *N Engl J Med*. 1992;327:1832–1835
- Centers for Disease Control and Prevention. Use of folic acid for prevention of spina bifida and other neural tube defects: 1983–1991. *MMWR*. 1991;40:513–516
- Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR*. 1992;41:1–8
- Forrest JD. Epidemiology of unintended pregnancy and contraceptive use. *Am J Obstet Gynecol*. 1994;170:1485–1489
- Moore KL. Formulation of the trilaminar embryo. In: *The Developing Human*. Philadelphia, PA: WB Saunders Co; 1988:55–64
- Centers for Disease Control and Prevention. Knowledge and use of folic acid by women of childbearing age—United States, 1995 and 1998. *MMWR*. 1999;48:325–327
- Hall JG, Solehdin F. Genetics of neural tube defects. *Ment Retard Dev Disabil*. 1999;4:269–281
- Smithells RW, Nevin NC, Seller MJ, et al. Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet*. 1983;1:1027–1031
- Cornel MC, Erickson JD. Comparison of national policies on periconceptional use of folic acid to prevent spina bifida and anencephaly. *Teratology*. 1997;55:134–137
- Bailey LB. Folate requirements and dietary recommendations. In: Bailey LB, ed. *Folate in Health and Disease*. New York, NY: Marcel Dekker, Inc; 1995:123–151
- Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects: implications for prevention. *JAMA*. 1995;274: 1698–1702
- Institute of Medicine. Dietary reference intakes: folate, other B vitamins, and choline. In: *Dietary Reference Intakes for Thiamin, Riboflavin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press; 1998:(8)32
- US Department of Health and Human Services, Food and Drug Administration. Food standards: amendment of the standards of identity for enriched grain products to require addition of folic acid. *Federal Register*. 1996;61:8781–8807
- Oakley GP. Let's increase folic acid fortification and include vitamin B<sub>12</sub>. *Am J Clin Nutr*. 1997;65:1889–1890
- Oakley GP Jr, Erickson JD. Vitamin A and birth defects: continuing caution is needed. *N Engl J Med*. 1995;333:1414–1415
- Tolmie J. Neural tube defects and other congenital malformations of the central nervous system. In: Rimoin DL, Connor JM, Pyeritz RE, eds. *Emery and Rimoin's Principles and Practice of Medical Genetics*. New York, NY: Churchill Livingstone Inc; 1997:2145–2176

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