Folic acid: when to supplement and by how much

Ged O’Connor1 and Colin P. Doherty2,3,4

Affiliations: 1Department of Neurology, Beaumont Hospital, Dublin 9, Ireland; 2Department of Neurology, St James’s Hospital, Dublin 8, Ireland; 3Department of Clinical Neurological Sciences, RCSI, Dublin, Ireland and 4Lecturer in Clinical Medicine, Trinity College, School of Medicine, Dublin, Ireland

ABSTRACT

INTRODUCTION

Folate is a water-soluble B vitamin, found particularly in such foods as leafy green vegetables and citrus fruits. Folic acid is the synthetic form of the vitamin. The value of pre-conceptual dietary supplementation with folic acid in women of child bearing age in reducing major congenital malformations (MCMs) and neural tube defects (NTDs) has been demonstrated in a number of large studies. However, the role and dosing of folic acid in women with epilepsy (WWE) who are taking anti-epileptic medication (AEDs) is less clear.

OBJECTIVE

To review the role of folate in the development of the neural tube and the evidence underlying the recommendations for folic acid supplementation in women of child bearing age and in WWE.

METHODS

We performed a formal literature search and from the results we reviewed the available studies and guidelines on the use of folic acid in the general population and in WWE.

CONCLUSION

Standard dose (0.4 mg) of folic acid use should be encouraged in all women of childbearing potential, but the evidence to support the use of high-dose (ie, 5 mg) folic acid in women who do not have a personal or family history of NTD/MCM occurrence is not strong. The evidence that folic acid supplementation will protect WWE from MCMs and NTDs is poor. However, given the potential interference in the metabolism of folate by some AEDs, high dose folic acid (5 mg) should be prescribed in WWE but only in those without a personal history of malignancy.

Keywords: folic acid, women with epilepsy, supplementation, major congenital malformations

INTRODUCTION

In 1931, Dr. Lucy Wills demonstrated that yeast extract was effective against the tropical macrocytic anemia seen in late pregnancy in India.1 In the subsequent decade, the compound responsible for this effect, folate, was isolated. Folate is a water-soluble B vitamin, found particularly in such foods as leafy green vegetables, citrus fruits, and legumes. Folic acid is the synthetic form of the vitamin, which is given as a supplement or added to fortified foods. The value of preconceptual dietary supplementation with folate in women of child bearing age in reducing major congenital malformations (MCMs) and neural tube defects (NTDs) has been demonstrated in a number of large studies. This has led to explicit guidelines from the American Academy of Neurology (ANN) and the European Registration of Congenital Anomalies and Twins (Eurocat) regarding such supplementation and fortification,2,3 and has led to folic acid fortification of food in many countries as a public health measure for the reduction of NTD occurrence rates.4

The role and dosing of folic acid in women with epilepsy (WWE) who are taking antiepileptic medication (AEDs) is less clear. Some AEDs can theoretically interfere with folate metabolism, thus presumably increasing the risk of both MCM and NTD occurrence. Despite the lack of convincing evidence for a protective effect of folate supplementation in WWE, guidance from organizations such as the American Epilepsy Society (AES)5 and the National Institute for Clinical Excellence5 in the UK have strongly recommended it.

In the course of this article, we will review some of the basic mechanisms of folic acid metabolism, the role of folate in the development of the neural tube, and the evidence underlying the recommendations for folic acid supplementation in women of child bearing age and in WWE. We will examine the evidence that these recommendations have been shown to affect the outcomes of pregnancy in WWE and whether folic acid in itself is associated with any adverse outcomes in the doses recommended.
METABOLISM

In adults (aged 19 or older) the recommended daily allowance (RDA) of folate in the diet is 400 μg per day, rising to 600 μg in pregnancy, and 500 μg during lactation. There is a difference in bioavailability of folate and the synthetic preparation folic acid, such that the equivalent RDA of folic acid is 240 μg per day, rising to 360 μg in pregnancy.

Dietary folate is initially hydrolyzed from the polyglutamate forms to monoglutamate forms in the intestinal wall. Absorption occurs through the jejunum and much of the monoglutamate is taken up from the portal circulation into the liver. In the liver, monoglutamyl folate is first reduced by dihydrofolate reductase to a dihydrofolate compound and then reduced further to tetrahydrofolate (THF). Subsequent to the formation of THF, 5,10-methylene-THF is formed by the addition of methylene groups from one of serine, glycine, or formaldehyde (see Figure 1). The 5,10-methylene-THF is subsequently converted into 5-methyl-THF through the action of methylene tetrahydrofolate reductase (MTHFR). The 5-methyl-THF serves to replenish the methylated form of vitamin B12, which is a cofactor for methionine synthase. This is the enzyme that converts homocysteine to methionine, which is then converted to S-adenosyl-L-methionine (SAM), the principal methyl donor for DNA methyltransferases.

NEURAL TUBE DEVELOPMENT

Folic acid has received the most attention in the prevention of NTDs and MCMs. However, to appreciate the importance of folate in this process, it is important to review the normal process of neural tube formation in the development of the central nervous system.

In the development of the embryo, the primitive streak develops by embryonic day 13, elongates until day 16 and then regresses until day 28. During this regression, primitive notochordal cells ingress to form the notochordal canal by approximately day 16. This structure is further modified over subsequent days and, by day 25, has become the true notochord.

Under the influence of soluble growth factors secreted by the developing notochord, ectodermal cells are induced to form neuroectoderm, which then forms the thick and flat neural plate above the notochord. As this develops, the process of primary neurulation begins, usually at embryonic day 17. This process is responsible for forming brain and the majority of the spinal cord. As a result of the expanding epidermis, the neural plate folds, giving rise to the neural groove as a midline furrow (see Figure 2) and the neural folds elevated laterally. The process continues with the formation of the paired lateral hinge points, and pressure on these hinge points causes convergence of the neural folds toward the midline and fusion of the neural folds. Fusion of the neural folds begins near the cervicomедullary junction at about embryonic day 20 and then proceeds both cranially and caudally. The last two points of closure are the cranial neuropore at day 24 postovulation and the caudal neuropore at day 26.

The process of secondary neurulation begins after this and forms the spinal cord caudal to S2, but is less organized than primary neurulation. In this process, a cell population at the caudal extremity of the primitive streak differentiates and forms a neuroepithelium surrounding a central cavity. The neural tube formed by this process then fuses with the primary neural tube more rostrally.

The role of folic acid in this process is speculative and whether folic acid is any more pivotal than any other neurochemical remains unclear. Nevertheless, the high rate of neural cell division that occurs during the highly structured primary neurulation phase suggests that methylation, via folate metabolism, of proteins and lipids is crucial. It is likely therefore that interruptions in this process, whether due to

![Figure 1](image1.png)

**Figure 1.** Folate acid metabolism and role in nucleic synthesis. 5,10-Methylene tetrahydrofolate (THF) is required for the synthesis of nucleic acids, while 5-methyl THF is required for the formation of methionine from homocysteine. Methylen THF reductase is an enzyme required to catalyze the reduction of 5,10-methylene THF to 5-methyl THF.

![Figure 2](image2.png)

**Figure 2.** Events of primary neurulation. At day 17, the neural groove forms. Over the subsequent days, the neural folds become elevated laterally and approach the midline. Fusion begins at the cervicomедullary junction at about day 20 and is completed by day 24–26.
genetic or environmental factors, are an important cause of NTDs. The epidemiological and scientific evidence is reviewed below.

**FOLIC ACID SUPPLEMENTATION AND MCMS/NTDS**

The spectrum of NTDs is considerable, and some—such as anencephaly—are incompatible with life. The NTDs are a considerable cause of neonatal mortality and morbidity worldwide, with an estimated incidence of more than 300,000 new cases per year.9 Over 95% of these cases are a first occurrence.10,11

There are numerous possible mechanisms for NTD formation in humans (Figure 3). Genetic factors clearly play a significant role in some cases. The recurrence risk of NTD in siblings of index cases is 2%-5%—approximately 50 times more than in the general population.12 Some studies have suggested that 70% of the variance in NTD prevalence may be due to genetic factors,13 but twin studies of NTD frequency have suggested a lower contribution.14

Most NTDs show sporadic occurrence and this suggests a multifactorial polygenic or oligogenic pattern of inheritance. In the studies carried out thus far on candidate genes causative of NTDs, the most robust findings are the two genetic polymorphisms in the MTHFR gene, C677T and A1298C.15,16

However, it is clear that genetic factors alone are not responsible for NTD formation. As an example, mice whose genetics have been engineered to disrupt methionine synthesis (MTHFR-null mice) do not develop spinal defects.17 Similarly, the increased rate of NTD formation with the polymorphisms specified above is not seen in all populations.18 It is likely that there is a genetic predisposition to NTD formation that then requires an environmental factor for this to manifest. This is suggested by studies in mice, where folate deficiency causes NTDs only in the setting of a genetic predisposition.

Environmental factors associated with increased NTD occurrence include season of conception,19 socioeconomic class,20 maternal diabetes,21 maternal age,22 maternal alcohol abuse,23 and maternal use of certain medications (in particular, sodium valproate).24 Deficiency states, such as folate or vitamin B12 deficiency, are also associated with NTD occurrence.25,26 More recently, maternal smoking and exposure to smoke have been associated with an increased rate of NTDs.27

Of the environmental factors mentioned above, folate deficiency has been extensively investigated. Although the mechanisms by which folate deficiency leads to NTD formation are not fully understood, it is clear that in the normal process of cell formation, methylation is needed for synthesis of membrane phospholipids and myelin basic protein.28,29 It has been demonstrated that folate deficiency is associated with global DNA hypomethylation30 and an increased rate of malformations.31 The reasons why the developing nervous system is particularly vulnerable to the effects of folate deficiency compared to other tissues are not fully understood. Precursor cells for both the neural crest and neuroepithelial cells have a higher level of folate receptor expression than others.32 Given this and the rapid growth and differentiation seen during gastrulation and neural tube formation, these features may explain why folate deficiency seems to be particularly detrimental to the nervous system.

The beneficial role of periconceptual folic acid supplementation in the prevention of NTDs has been demonstrated in a number of trials.33-35 A recent meta-analysis of the published data35 estimated that folic acid supplementation can give a reduction in the first occurrence of NTD of 62%. The estimated effect of folic acid fortification of food products in the prevention of NTD is 46%. Data from randomized trials suggest that folic acid supplementation is effective in 70% of cases in the prevention of recurrent NTD.

However, there are difficulties in the interpretation of studies on the protective effects of folic acid supplementation. The dose of folic acid used in studies varies, from 0.36 mg to 5 mg per day.36 The designs of these studies are often quite different, ie, randomized controlled trials35 versus observational studies,37 and direct comparisons can be difficult. Overall, however, the benefits of folic acid supplementation are felt to be clear-cut for the general population of women of child bearing age,4 to the extent that many countries have initiated fortification of foods with folic acid.

Figure 3. Intake of B vitamins other than folate also affects folate metabolism. This process can also be disrupted by genetic variants. Disruption of the methylation of lipids, DNA, and proteins during early embryogenesis could lead to NTDs. It is proposed that folate prevents NTDs by increasing methylation of various molecules that are essential to cellular processes.
as a public health measure.\textsuperscript{38} Such fortification has been justified on the basis of the benefits of folic acid supplementation and the limited impacts of public health campaigns in ensuring preconceptual folic acid use. Previous studies of public health\textsuperscript{59} and mass media campaigns\textsuperscript{40} have shown that these methods are not successful in increasing folic acid use in women in the long term.

It should be noted that the benefit of folic acid supplementation may be limited in the prevention of NTDs. In one recent observational study after the introduction of folic acid fortification in some European countries, the rate of NTD occurrence fell to 7 or 8 cases at birth or abortion per 10 000 births, suggesting a “floor effect” for the potential benefits seen.\textsuperscript{43}

Folic acid supplementation has also been shown to cause a reduction in MCMs beyond NTDs. It has been shown that folic acid supplementation can reduce the rate of congenital heart defects, limb defects, and anomalies of the urinary tract.\textsuperscript{44} There is also a growing body of evidence that folic acid supplementation may also be associated with a lower rate of certain childhood malignancies,\textsuperscript{45,46} although the evidence for this is not as robust as other findings.

**PREGNANCY IN WWE**

While there appears to be at least some robust evidence in favor of folic acid as a periconceptual supplement in women in the general population, to what extent this can be applied to WWE is unclear. It has been recognized for many years that epilepsy and its treatment have significant implications for both maternal and fetal health. A PubMed search for publications relating to maternal epilepsy and congenital malformations reveals over 500 citations. Initial reports go back to the 1960s noting the link to anticonvulsant treatment and malformations.\textsuperscript{47} There are many reports in the literature of complications associated with epilepsy in pregnancy including increased rates of caesarean section, preterm delivery, and low birth rate.\textsuperscript{38,49} However, based on more recent data from a number of pregnancy registries, it is now accepted that the vast majority of WWE will have uncomplicated pregnancies.\textsuperscript{50,52}

The issue of NTDs/MCMs in pregnancy in WWE is one that is complicated by a number of factors. The frequency of MCM in pregnancies of women without epilepsy varies, but has been reported in studies as approximately 1.6–2.1%.\textsuperscript{53–58} In WWE not taking AEDs, the rate of MCM is estimated to be slightly higher (2.8%) although clearly the numbers used for these estimates is considerably lower.\textsuperscript{54} The effect of AED therapy on the rate of NTDs or MCMs is also variable and depends greatly on the medications used. Rates as low as 0% with levetiracetam monotherapy have been reported (but again with very small numbers),\textsuperscript{55} compared to as high as 17.1% with sodium valproate monotherapy.\textsuperscript{54,55} Polypharmacy is associated with a higher rate of MCMs than monotherapy.\textsuperscript{57} The mechanisms of NTD formation by AEDs are still largely unknown. Some of the AEDs, such as phenytoin, carbamazepine and primidone, are metabolized by the CYP450 system in the liver. These enzyme-inducing drugs can interfere with the action of MTHFR,\textsuperscript{58} thus impairing folate metabolism and action. However, this clearly cannot be the principal mechanism, as sodium valproate is not an enzyme-inducer and has the greatest rate of teratogenic complications.

There are risks seen in relation to not taking AEDs during pregnancy. It has been shown that even complex partial seizures can induce fetal bradycardia.\textsuperscript{59} Trauma related to seizures and status epilepticus appear to be major causes of excess maternal mortality in WWE.\textsuperscript{60} There are also reports of excess fetal loss in WWE not taking AEDs.\textsuperscript{61} Given the dangers of uncontrolled seizures to both the mother and the fetus, all guidelines recommend the continuation of AED therapy during pregnancy.

Generally, WWE are seen as being a high risk group for the occurrence of MCMs and NTDs in pregnancy. The guidelines from the various national and international federations reflect this, as they recommend the use of folic acid in all cases.\textsuperscript{2,5} Many authors have expressed the opinion that the higher doses of folic acid available (4–5 mg) should be used, instead of the 0.4 mg dose that is recommended for lower risk groups.\textsuperscript{62,63} However, the evidence to support this is lacking.

There has been concern that the adverse effects of AEDs in causing MCMs are not amenable to prevention by folic acid supplementation. In a paper this year, those WWE who were on high-dose (5 mg) preconceptual folic acid did not have a lower rate of MCMs than those who were not.\textsuperscript{64} The lack of effectiveness of folic acid has also been shown in results of trials from the UK pregnancy registry and from other sources.\textsuperscript{65} In contrast to this, the findings from other registries have suggested that the use of folic acid reduced but did not eliminate the rate of MCMs in pregnancy in WWE.\textsuperscript{66} It has also been reported that the use of folic acid has been associated with a lower rate of spontaneous abortions, especially in those on sodium valproate.\textsuperscript{57}

In short, it can be said that folic acid supplementation should be used in WWE, based more on the data from studies in the general population rather than on clearly demonstrated efficacy in trials on populations of WWE. It is unclear why the effects are not as clear-cut in WWE. It is recognized that the mechanism of teratogenicity of AEDs is not limited to interference with folate metabolism, and this may explain why the results of high-dose folic acid as a protective agent are somewhat disappointing. Nevertheless, the use of high-dose folic acid continues to be recommended as such doses may maximize any potential benefit. However, it is worth reviewing the question of the potential harm associated with high-dose folic acid.

**POTENTIAL ADVERSE EFFECTS OF FOLIC ACID SUPPLEMENTATION**

Previously, the principal concern with the use of folic acid has been the potential masking of vitamin B12 deficiency, leading to a delay in diagnosis. Folic acid supplementation can correct the laboratory abnormalities of vitamin B12
deficiency, allowing the adverse effects of the deficiency to progress undetected until much later.

Folic acid has been studied in areas other than the prevention of NTDs. Given the effects it has on lowering homocysteine levels, it has been proposed that it may be of use in the prevention of vascular events such as stroke and myocardial infarction,\(^{58}\) and it has been proposed as a protective agent against a number of cancers.\(^{59}\) Some of the observational studies and trials to assess this potential use have raised concerns about the use of folic acid, especially in supraphysiological doses.

Epidemiological studies in cancer prevention have suggested that higher folate status is associated with a decreased risk of a number of cancers including those of the colon, pancreas, and stomach.\(^{59}\) Studies on folate status and colorectal cancer suggest a 20%-40% reduction in adenoma or cancer rate in those with the highest status.\(^{70,71}\) Small trials have also shown that folic acid supplementation can decrease adenoma recurrence rate after resection.\(^{72}\) However, other trials have not shown any significant effect.\(^{73}\)

The concern is whether the use of folic acid, especially in supraphysiological doses, could be associated with increasing the risk of malignancy. Epidemiological studies from the United States have shown an increase in the incidence of colorectal cancer after the introduction of folic acid dietary fortification.\(^{74}\) The results of the Aspirin/Folate Polyp Prevention Study seemed to suggest a potential tumor-promoting effect of folic acid supplementation. In this trial, the use of folic acid seemed to be associated with an increased risk of developing advanced lesions with malignant potential and of developing any other cancer.\(^{75}\) Animal studies of this question would seem to offer an explanation of such results. In animal models, folate deficiency in normal colorectal mucosa seems to promote tumor genesis but in established neoplasms, folic acid supplementation seems to promote tumor progression.\(^{59}\)

In studies of cancers outside of the colorectum, a prospective study showed that increased folate plasma concentrations were associated with an increased risk of premenopausal breast cancer (although the result was not felt to be statistically significant),\(^{76}\) and a prospective cohort study showed an increased risk of postmenopausal breast cancer in those whose folate consumption was highest.\(^{77}\) However, other studies have generally shown a protective effect on folate intake against breast cancer.\(^{78}\) In two prospective cohort studies, multivitamin use (containing folic acid) was associated with a nonsignificant increased risk of pancreatic cancer.\(^{79}\) How much these results are due to the dose of folic acid, or on the use folic acid supplements rather than dietary folate, is unclear, and it should be noted that in many cases the results did not reach statistical significance.

CONCLUSION

There is no doubt about the benefit of folic acid use in the population as a whole. Neurologists should be aware of this and should be more active in the use or prescription of folic acid for WWE. It has been shown in a number of studies that the guidelines for preconception counseling and the use of folic acid are not well adhered to by both neurologists and other specialists. However, specifically on the issue of dosing, the evidence available does not support the use of high-dose folic acid in those women who do not have either a personal or family history of NTD or MCM occurrence. Furthermore, in some patients, the use of folic acid may not be as risk free as is commonly supposed. From our current reading of the available evidence, the following points should be considered:

1. Standard dose (0.4 mg) of folic acid use should be encouraged in all WWE of child bearing potential.
2. The evidence to support the use of high-dose (i.e., 5 mg) folic acid in WWE who do not have a personal or family history of NTD/MCM occurrence is not strong.
3. The evidence that folic acid supplementation will protect WWE from MCMs and NTDs is poor. However, given the potential interference in the metabolism of folate by some AEDs, high-dose folic acid (5 mg) should be prescribed in WWE but only in those without a personal history of malignancy.
4. Folic acid should be used in those with a history of malignancy only with caution, after a full discussion of the possible benefits and risks, and with regular review.

The rate of NTD occurrence can be lessened, but not eliminated by the use of folic acid, a fact that patients should be made aware.

Disclosures: The authors have no disclosures or conflicts of interest and funding.

REFERENCES

5. The epilepsies; the diagnosis and management of the epilepsies in adults and children. Epilepsy NICE guideline October 2004. www.nice.org.uk


De Bree A, Verschuren W, Kromhout D, Kluitmans A, Blom H. Homocysteine determinants and the evidence to what extent


