The MOSS NUTRITION REPORT

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Product Review

June 2021 #347

FOLIC ACID SUPPLEMENTATION, UNMETABOLIZED FOLIC ACID, & METHYLTETRAHYDROFOLATE (MTHF) REVISITED

INTRODUCTION

Over the years I have written and lectured extensively on two vastly underappreciated issues that relate to folate metabolism and its impact on human health. First, folic acid - which has traditionally been assumed by virtually all of the public and allopathic practitioners plus all too many in the nutritional community to be just another term for folate that is naturally found in whole foods - is actually a synthetic compound that, even though it is molecularly very different from the food folate molecule, is close enough from a molecular structure standpoint to function reasonably well in folate/methylation pathways. However, please notice again the use of the word "reasonably." More on that shortly. Second, while the use of folic acid as a processed food fortifier and component of many supplements is quite ubiquitous due to its shelf-life stability and low cost compared to food folate, its positive impact is limited to fairly small amounts in the range of 200 – 400 mcg per day. Why is this an issue? Because the use of folic acid is so prevalent in processed foods and supplements, it has become increasingly common for many if not most of the American public to be consuming amounts well above 200 – 400 mcg per day. This, in turn, becomes an issue because the body has only a limited capacity to metabolize folic acid, due to the fact it is, at heart, a synthetic compound that bears only a similarity to food folate from a molecular standpoint. The net result is that, in dosages of folic acid above 400 mcg per day, the appearance of unmetabolized folic acid in the circulatory system will be inevitable.

Several published papers over the years (many of which I have highlighted in both my writings and lectures) have made it clear that, in reality, folic acid, a synthetic analog of food folate, only acts like a nutrient in low doses. In the high doses that are increasingly more common in the American population, folic acid acts more like a drug in that it can, in its unmetabolized form in the human body, perform as a major enzyme inhibitor, mainly inhibiting methylation enzymes such as dihydrofolate (DHFR) reductase and methyltetrahydrofolate reductase (MTHFR). How does the inhibiting properties of high dose folic acid impact clinically? Several studies have suggested that this inhibition by unmetabolized folic acid can affect many different metabolic pathways, including neurologic development both in utero and after birth, possibly contributing to the increases in autism spectrum disorders that, statistically, have been increasing in prevalence since food fortification with folic acid was instituted in 1998. Thus, ironically, the low doses of folic acid that have been so successful in reducing the incidence of neural tube defects may actually create neurologic developmental defects of a different but clinically equal magnitude in high doses.

Fortunately, the concern about excessive intake of folic acid has been slowly gaining traction in the supplement industry, with more and more supplement companies either eliminating folic acid from their products in favor of natural forms of folate such as methyltetrahydrofolate (MTHF) or reducing the amount of folic acid in

their products. However, supplements containing very high amounts of folic acid, i.e., 4 mg of folic acid per cap or tablet, which are guaranteed to lead to significant amounts of unmetabolized folic acid in the circulatory system, can still be found in the marketplace. Why? There still is a belief in the medical community that, for women at high risk for bearing children with neural tube defects, 4 mg per day of supplemental folic acid with no regard for the amount of dietary folic acid from processed foods, is the optimal dose. Should this recommendation be abandoned? The two papers I am about to review, both published in respected peer-reviewed journals, make a very compelling case that the answer to this question is a resounding yes. In turn, while the papers I am about to review do not make a specific alternative recommendation, it is my opinion that, if the decision is made for any particular woman that 4 mg per day is absolutely essential, the use of an MTHF product such as **L-5-MTHF** from Moss Nutrition should be considered.

WHY WOMEN AT HIGH RISK FOR BEARING CHILDREN WITH NEURAL TUBE DEFECTS AND THE PHYSICIANS WITH WHOM THEY CONSULT MUST DISCARD THE 4 MG PER DAY FOLIC ACID RECOMMENDATION

The first paper I would like to review that makes the case against 4 mg per day is "Impact of high-dose folic acid supplementation in pregnancy on biomarkers of folate status and 1-carbon metabolism: An ancillary study of the Folic Acid Clinical Trial (FACT)" by Murphy et al (Murphy MSQ et al, *Am J Clin Nutr*, Vol. 113, No. 5, pp. 1361-1371, May 2021). In this paper the results of a study were presented where women who were pregnant from 8 -16 weeks were evaluated. The women were divided into two groups. The first, the high dose group consisting of nineteen women, consumed a supplement containing 4 – 5.1 mg folic acid (FA) per day until delivery. The second, the low dose group consisting of 31 women, consumed a supplement containing equal or less than 1.1 mg per day until delivery. The first quote I would like to feature from the paper provides some foundational information on the history of supplemental folic acid dosing to pregnant women:

"Women at low risk for a neural tube defect (NTD)-affected pregnancy are advised to consume a daily multivitamin containing 400 µg FA in Canada and 400 – 800 µg FA in the United States. For women at high risk for having an NTD-affected pregnancy, many health professional organizations recommend higher FA doses in the range of 4.0-5.0 mg. At issue is which women stand to benefit from higher doses, given the variable definitions among organizations and jurisdictions for who is at high risk for an NTD-affected pregnancy."

Of course, as I mentioned, the major downside of high dose folic acid supplementation is that most women who consume processed foods that are fortified with folic acid is that, even without supplementation, they demonstrate high levels of unmetabolized folic acid (UMFA):

"Although FA supplementation is effective at increasing RBC and serum total folate concentrations, circulating unmetabolized FA (UMFA) is ubiquitous in populations consuming fortified foods, and high UMFA concentrations are commonly observed among pregnant and postpartum women."

Why is this a concern? As I suggested above, UMFA may be a significant enzyme inhibitor:

"It has been hypothesized that UMFA, through its metabolism to dihydrofolate, can impair folate-mediated 1-carbon metabolism by inhibiting key folate-dependent enzymes."

What were the results of the study? First, as you might expect, the high dose group had higher serum total folate concentrations than the low dose group. Unfortunately, analysis of the composition of the serum folate indicated that the higher serum folate levels were due to

both bioactive 5-MTHF and metabolically useless and potentially harmful UMFA:

"Our findings demonstrate that women who initiate daily high-dose FA supplementation (4.0-5.1 mg) between 8 and 16 gestational weeks have higher serum total folate concentrations at 24-26 gestational weeks than women taking low-dose FA supplements (≤1.1 mg). The higher serum total folate concentrations in women taking high-dose FA were attributable to both higher UMFA and 5-methylTHF concentrations."

Did MTHFR or other SNPs have any impact on the findings? The authors did consider this possibility and found that this issue was not relevant to the findings:

"Genotype distributions of common SNPs in 1-carbon metabolism-related enzymes (MTR, MTHFR, MTHFD1) that could potentially influence the distribution of folate vitamers also did not differ between groups."

Concerning the level of UMFA in the high dose group, how high was it compared to a typical population of pregnant women consuming 1 mg per day of FA? As you will see from the next quote, the level was significant:

"…UMFA in participants consuming 4.0-5.1 mg FA was 2 times higher than women at 12-16 gestational weeks taking 1 mg/d since early pregnancy…"

Then, if that was not bad enough, consider the following very sobering statistics about the levels of UMFA in the high dose group:

"Serum UMFA concentrations in the high-dose group were also above the 90th percentile reported for the general US population. In addition, UMFA represented a higher proportion of serum total folate in the high-dose group, consistent with another study that found UMFA disproportionately increased when serum total folate exceeded 78.5 mmol/L in women consuming 1 mg/d FA from early pregnancy to 8 wk postpartum."

The next quote provides much more detail as to why there is so much concern in the research community about high levels of UMFA induced by folic acid supplementation:

"While the functional ramifications of circulating UMFA are largely unknown, it has been associated with, albeit inconsistently, reduced natural killer cell cytotoxicity. FA supplement use in pregnancy has also been associated with asthma and respiratory tract infections among exposed children. UMFA is hypothesized to inhibit folate-mediated metabolism through the inhibition of key enzymes, which could manifest as altered distributions of folate vitamers or functional folate deficiency indicated by higher homocysteine. For example, in vitro studies demonstrate that MTHFR can be inhibited by dihydrofolate, the product of the dihydrofolate reductase reduction of FA. Inhibition of MTHFR activity could replicate the effects of the *MTHFR* 677C > T SNP, which reduces enzyme activity and is associated with lower 5-methylTHF and higher nonmethylated folates in RBCs, as well as hyperhomocysteinemia."

With all the above in mind, Murphy et al conclude that, even though the levels of FA supplementation in the high-dose FA group were not linked with any specific harm clinically, there was no evidence of any additional benefit. Furthermore, the high levels of UMFA seen with the high-dose group were deemed "supraphysiologic" by the authors:

"Although our findings do not indicate harm, they also do not demonstrate additional benefit given that all of the women exceeded the WHO cutoff for NTD risk reduction. Furthermore, the high UMFA concentrations suggest that the high-dose FA was supraphysiologic."

In turn, the authors, in no uncertain terms, recommend against high-dose FA supplementation in pregnant women, regardless of NTD risk:

"Given that the FACT trial showed no effect of high-dose FA on preeclampsia risk, and we show here that there is no benefit from a metabolic perspective, high-dose FA is unwarranted for this clinical population."

The second paper I would like to review is even more directly adamant that supplementing women at high risk for NTDs with 4 mg per day of FA is certainly unnecessary and clearly

excessive. The first quote I would like to feature from "Folic acid supplementation to prevent recurrent neural tube defects: 4 milligrams is too much" by Dolin et al (Dolin CD et al. *Fetal Diagn Ther*, Vol. 44, pp. 161-165, 2018) discusses recommendations from the US Preventive Services Task Force (USPSTF):

"The US Preventive Services Task Force (USPSTF) recommends a daily supplement of 400 – 800 µg of folic acid for all women who are planning or capable of pregnancy. A much larger supplement of 4 mg is recommended for women considered at high risk for an NTD, particularly those with a previous pregnancy complicated by an NTD."

The next section of the paper I would like to highlight provides the very curious history of the origin of the 4 mg recommendation:

"Laurence et al. conducted one of the first randomized clinical trials to report that folic acid supplementation reduced the risk of a recurrent NTD (i.e., women who had a previous pregnancy complicated by an NTD). In this study, women assigned to the treatment group received a daily 4-mg supplement of folic acid prior to conception through early pregnancy."

Unfortunately and ironically, no rationale was given as to how the 4 mg dose was decided upon:

"The rationale for choosing this dose was not provided by the authors, and no other doses were tested."

Therefore, the authors never considered the possibility that good results could be obtained with lower doses. However, in fairness, the study was published in 1981, long before the dangers of UMFA were discovered. In turn, there was little incentive to determine the lowest possible effective dose. Nevertheless, it did not take long for researchers to assume that this very arbitrary decision by Laurence et al. about 4 mg per day of FA for women at high risk for NTDs had mysteriously become irrefutable fact. This was evidenced by a follow-up study in 1991:

"In 1991, the Medical Research Council (MRC) Vitamin Study Research Group published a large, multicenter randomized clinical trial demonstrating that 4 mg of folic acid supplementation beginning prior to conception decreased the risk of recurrent NTD by 71%, equivalent to a 3.5-fold protective effect. The findings of this study were considered definitive in supporting high-dose folic acid supplementation among women at increased risk for an NTD…"

Unfortunately, the MRC made the same mistake as Laurence et al. No other doses were tested:

"…the 4-mg dose was the only dose administered at the trial."

What rationale did the MRC give for using the 4 mg dose:

"The MRC's rationale for selecting this high dose was based on the findings of Laurence et al. and also concern that if lower doses were selected, and findings were inconclusive, then they might not have had the opportunity to repeat the study with a higher dose."

As you might expect, even though no researcher had ever considered the possibility that similar results could be obtained with smaller doses, the public health community, subsequent to the MRC study, jumped on the 4 mg dose bandwagon:

"In 1991, in response to the impressive findings of the MRC study and smaller studies, the Centers for Disease Control and Prevention (CDC) recommended that women with a previous pregnancy complicated by NTD should take a daily 4-mg supplement of folic acid prior to future pregnancies."

To their credit, the CDC, in an editorial, did issue a disclaimer of sorts indicating that this was an interim recommendation:

"Given that 4 mg of folic acid is 20 times the recommended daily allowance (RDA) for nonpregnant women and other studies had found protective benefits using smaller doses of folic acid, an editorial note in 1991 stated that the 4-mg dose was 'an interim recommendation, pending further research.'"

Unfortunately, it appears, all these years later, that this "further research" never occurred as the 4 mg recommendation continues to be policy for women at high risk for NTDs:

"Yet, nearly 30 years later, the recommendation remains. Currently, there are extremely limited data regarding the efficacy of folic acid supplementation above ~1 mg in the prevention of NTDs, particularly among high-risk women."

In addition:

"Among women who are not considered high risk, doses of 400 to 800 µg folic acid have consistently been shown to effectively reduce the risk of NTDs, and doses above 1 mg do not provide any additional protective benefit."

Next, Dolin et al discuss why 4 mg is too much. They begin this discussion by going into detail about the difference between folic acid and natural, food-based folate:

"Though sometimes used interchangeably, folate and folic acid are not synonymous. Folic is a water-soluble B vitamin (vitamin B_9) that naturally occurs in foods, such as legumes, citrus, and green leafy vegetables. Folic acid is the synthetic, oxidized form of the vitamin used in supplements and fortified foods. The bioavailability of folic acid and folate differs greatly. Folic acid, which is already in an active monoglutamate form, is almost completely bioavailable, especially when administered on an empty stomach. Food folate is present in a polyglutamate form and must be digested to monoglutamates prior to absorption, resulting in ~50% bioavailability."

Before continuing, I would like to comment on bioavailability. It is indeed unfortunate that many in the nutritional community assume in a kneejerk fashion that higher absorption is always better. In the case of folic acid versus food folate, this is decidedly not the case. In reality, ingested substances are very often most efficaciously and safely used by the body when they pass through the somewhat slow and various digestive and metabolic steps that assure, no matter how much is ingested, the right amount of the ingested substance goes to the right place in the body at the right time.

This is certainly true for food folate, making it extraordinarily safe and effective even in fairly high doses. Furthermore, when natural folate in the form of L-5-MTHF supplements are ingested, the safety window is much broader than what is seen with folic acid - because it goes through many of the processes described above. Why? When folic acid is ingested, because it is synthetic, the body really has little idea what to do with it. Therefore, it is absorbed quickly at virtually a 100% rate. After absorption, the body has a limited capacity to metabolize it into a form the body can use. In turn, because of this limited ability to metabolize folic acid, UMFA can quickly build up, creating a much narrower safety window.

In the next quote, Dolin et al describe some of the metabolic steps for food folate mentioned above and how folic acid differs:

"Folate-binding proteins and tubular re-absorption mechanisms within the kidneys, as well as the small intestine, retain needed folate and prevent losses. Excretion of folate occurs mainly through urine in the form of folate catabolites. When folic acid supplementation is excessive, unmetabolized folic acid can also accumulate in the serum. The exact dose at which this happens is not known and may differ between individuals. Studies in both nonpregnant and pregnant women show that folic acid doses greater than ~ 800-1,000 µg/day result in detectable levels of unmetabolized folic acid in both maternal and fetal blood samples."

What might be the clinical impact of high dose folic acid and the high levels of UMFA that inevitably follow? The authors comment:

"There is limited and inconsistent evidence to determine the adverse effects of high levels of folic acid supplementation for the mother or the fetus. Observational studies have reported increased risk of cleft palates, spontaneous abortion, impaired psychomotor development, and childhood respiratory issues with the use of high doses of folic acid. Intakes of 800 µg to 5 mg or folic acid from supplements have been associated with an increased risk of cancer development and mortality."

With all the above in mind, Dolin et al make the following, "in your face," conclusion:

"The recommendation of a daily 4-mg dose of folic acid to prevent recurrent NTDs was arbitrary and unjustified 25 years ago, but has continued as 'dogma' even in recent literature. There is currently no reliable evidence that it is more effective than 1 mg, or even less, in preventing primary and recurrent NTDs, particularly in the setting of food fortification."

The authors go on to suggest a much more logical, patient-specific, functional medicine approach to recommendations for folic acid during pregnancy:

"Consideration should be made to changing the clinical protocol used to treat women at risk for recurrent NTD to reflect a woman's individual physiological need for folate based on her folate status. Currently, high-dose folic acid supplements are prescribed to all at-risk women, without assessment of their folate status. We propose that clinicians measure RBC folate concentrations as part of routine pre-conceptional care and prescribe the necessary level of folic acid supplementation (up to 1.0 mg) according to a woman's individual needs, with the goal of achieving optimal folate concentrations for the prevention of NTD. This could be done without any additional information regarding folate/folic acid intakes, genetic variability in folate metabolism (i.e., MTHFR genotype), or other factor associated with high risk of NTD. However, for the majority of pregnancies which are unplanned given the adequate levels of folic acid documented in the vast majority of women, the same 400-800 µg daily dose would seem sufficient even for recurrent risk cases."

Dolin et al conclude that, again, there is really no place for high-dose folic acid supplementation during pregnancy:

"Our review of the evidence suggests that it is reasonable to use the much more readily available lower doses of folic acid."

SOME FINAL THOUGHTS

While I cannot emphasize the importance and timeliness of the two papers just reviewed, I would like to point out one glaring deficiency of both that you can probably guess – no mention was made of MTHF supplements. Undoubtedly, as you are probably aware from the many writings and lectures by both me and others, MTHF supplements have been demonstrated, in an extensive amount of research and anecdotal literature, to be much safer and at least as effective, if not more so, compared to folic acid supplements when used in conservative doses of 1-2 mg per day. Therefore, whenever possible, particularly in those patients who are already ingesting high amounts of folic acid due to a high refined, fortified food diet, please recommend as the preferred form of folate supplementation products such as **L-5-MTHF** from Moss Nutrition.

L-5-MTHF 120 Vegetarian Capsules

Product #: M093

*Methylated folate as natural 6S isomer to help support a healthy methylation cycle. 1 mg capsules.