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Folic Acid Supplementation to Prevent Recurrent Neural Tube Defects: 4 Milligrams Is Too Much

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Abstract
Some medical practices have been ingrained in custom for decades, long after "proof" that they were effective was established. It is necessary to periodically reevaluate these practices, as newer theories and research may challenge the evidence upon which they were based. An example is the decades' old practice of recommending a 4-mg (4,000-μg) supplement of folic acid to women who are at risk for recurrent neural tube defect (NTD) during pregnancy. This recommendation was based on findings from a randomized clinical trial in 1991. Since then, multiple studies have confirmed the utility of 400–800 μg of folic acid in lowering both primary and recurrent risks of NTDs, but no studies have established any further reduction in risk with doses over 1 mg. Current understanding of folic acid metabolism during pregnancy suggests that at higher doses, above ~1 mg, there is not increased absorption. Recent evidence suggests that 4 mg folic acid supplementation may not be any more effective than lower doses for the prevention of recurrent NTDs. Thus, we recommend that it is time for clinicians to reexamine their reliance on this outdated recommendation and consider using current recommendations of 400–800 μg per day for all patients in conjunction with assessment of maternal folate status.

Introduction

Neural tube defects (NTDs) are congenital malformations of the cranium or spine that result from failure of normal neural tube closure during early pregnancy [1]. NTDs are one of the most common congenital anomalies in the US with a prevalence of 6.5 per 10,000 live births during 2009–2011 [2]. Over the past 100 years, the incidence of NTDs has been steadily decreasing secondary to better nutrition and screening with maternal serum alpha-fetoprotein and now ultrasound [3].

NTDs are a multifactorial disorder, with risk factors of genetic predisposition and various environmental exposures, the most influential being low maternal pericon-

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ceptional folate intake [1]. The main sources of folate are naturally occurring folate in foods, dietary supplements of folic acid, and folic acid-fortified foods. In the US, cereal grain products have been fortified with folic acid since 1998 [3]. This fortification program has been highly successful in decreasing the incidence of NTDs in the US population, independent of consumption of additional folic acid supplements [2, 3].

The US Preventative 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 [4]. 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 [1]. Here, we re-evaluate the evidence supporting the recommendation of 4-mg supplements among women at high risk of NTD to determine if it is effective, or even necessary.

Folate/Folic Acid and Neural Tube Defects

Food fortification interventions and clinical trials consistently show that increasing women's intakes of folic acid during the periconceptional period results in a decrease in the prevalence of NTDs [5, 6]. However, the exact mechanisms by which folate may act to prevent NTDs have yet to be determined. Folate has a major role as a co-enzyme in numerous biochemical pathway involved in one carbon metabolism (methylation), including the synthesis of DNA, RNA, and certain amino acids. Greater amounts of folate are required during pregnancy because of the rapid rate of cellular and tissue growth and development for the mother, placenta, and fetus. Inadequate amounts of folate during this time may inhibit or impair DNA synthesis and other cellular processes that require methylation, which may have detrimental and irreversible effects on the growing fetus [1].

History of the 4-mg Recommendation

Laurence et al. [7] 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. The rationale for choosing this dose was not provided by the authors, and no other doses were tested [7]. 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 from this study were considered definitive in supporting high-dose folic acid supplementation among women at increased risk for an NTD; however, the 4-mg dose was the only dose administered in the trial [8]. The MRC's rationale for selecting this high dose was based on the findings of Laurence et al. [7] 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 [8].

In 1991, in response to the impressive findings of the MRC study and smaller studies [9–12], 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 [13]. 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" [13]. 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. 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 [5, 14–16], and doses above 1 mg do not provide any additional protective effect (Table 1) [15–17].

Folic Acid Metabolism Suggests 4 mg Is Too Much

Humans cannot make folate and must obtain it through dietary or supplemental sources. Though sometimes used interchangeably, folate and folic acid are not synonymous. Folate 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

Table 1. Risk of neural tube defects with folic acid supplement dosing

Publication	Study	Folic acid exposure	Risk of NTDs
Werler et al., JAMA, 1993 [16]	Case-control study of 3,051 women in US and Canada		*RR (95% CI)*
		<0.4 mg	0.5 (0.2–1.5)
		0.4 mg	0.3 (0.1–0.6)
		0.5–0.9 mg	0.9 (0.2–4.2)
		≥1 mg	0.4 (0.1–1.3)
Shaw et al., Epidemiology, 1995 [15]	Case-control study of 1,077 women in California		*OR (95% CI)*
		Any dose	0.60 (0.46–0.79)
		<0.4 mg	0.99 (0.56–1.80)
		0.4–0.9 mg	0.54 (0.31–0.72)
		≥1 mg	0.92 (0.54–1.60)
Moore et al., Epidemiology, 2003 [17]	Prospective cohort of 23,228 women in northeastern US		*RR (95% CI)*
		1–399 DFE	0.29 (0.07–1.2)
		400–799 DFE	0.41 (0.10–1.7)
		≥800 DFE	0.56 (0.24–1.3)

RR, relative risk; CI, confidence interval; OR, odds ratio; DFE, dietary folate equivalents.

folate is present in a polyglutamate form and must be digested to monoglutamates prior to absorption, resulting in ~50% bioavailability. Micronutrient deficiencies (i.e., zinc), combinations of foods being consumed in the meal (i.e., alcohol or vitamin C-rich foods), and food preparation methods (i.e., raw versus cooked or processed) can also influence food folate digestion and absorption [18].

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 excess folate occurs mainly through urine in the form of folate catabolites [18]. 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 [19, 20].

Optimal Folate Levels for Neural Tube Defect Prevention

Several methods, including blood and urinary biomarkers, have been used to assess folate catabolism and determine sufficient folate levels for the prevention of NTDs during pregnancy. Red blood cell (RBC) folate concentrations are often used as the primary indicator of adequate folate since they are correlated with liver and tissue folate stores, reflecting the previous 2–3 months' intakes. Though serum and plasma folate levels are used, they are not considered ideal measurements since they only reflect recent intakes and can fluctuate on a daily basis. Studies that have investigated associations of NTD risk with RBC folate concentrations consistently show a substantially lower risk among women with concentrations of 906 nmol/L or greater [21]. This concentration is recommended by the World Health Organization for women of reproductive age to reduce the prevalence of NTDs [22].

The effects of folate intake on blood and urinary excretion concentrations during pregnancy have also been investigated by a series of metabolic studies [23, 24]. Pregnant (~2nd trimester) and nonpregnant women were fed diets of 450 and 850 μg/day folic acid (provided as food folate and synthetic folic acid) for 12 weeks. RBC folate concentrations were measured, as well as levels of urinary folate catabolites and plasma homocysteine [23, 24]. Among all women, both 450 and 850 μg of folic acid resulted in RBC concentrations above 906 nmol/L; mean RBC concentrations were 1,453 (±252) nmol/L and 1,734 (±209) nmol/L for 450 and 850 μg, respectively. Urinary excretion rates of folate catabolites were also similar among all women. However, especially at the lower folate dose, pregnant women were more efficient in conserving folate compared to nonpregnant women. Higher rates of urinary excretion were observed among all women re-

ceiving 850 μg versus 450 μg, suggesting that saturation levels of folate reabsorption from the proximal tubular cells had been reached. Additionally, plasma homocysteine concentrations (high plasma homocysteine concentrations indicate low folate levels) were even lower in pregnant compared to nonpregnant women but did not differ by level of folate supplementation. This observation suggests that both 450 and 850 μg/day of folate met, or even exceeded, the dose necessary to maintain plasma homocysteine levels [23].

Potential Toxicity of Folate/Folic Acid

The United States Department of Agriculture (USDA) publishes dietary reference intakes for nutrients, including RDAs and tolerable upper intake levels (UL). The RDA of folate for women who are capable of pregnancy is 400 μg from supplements and/or fortified foods, in addition to the consumption of a varied diet containing food folate [25]. The RDA of folate during pregnancy is 600 μg [25]. The USDA defines the UL as "the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population" [25]. A concern about excessive folate is the potential to mask and exacerbate neuropathy in those with vitamin B_{12} deficiency [25]. Based on this risk, the UL of folate during pregnancy is 1 mg from supplements/fortified foods for women 19 years and older [25]. The UL is 800 μg /day for women 14–18 years old [25].

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 [26]. Intakes of 800 μg to 5 mg of folic acid from supplements have been associated with an increased risk of cancer development and mortality [27].

Food fortification may substantially contribute to women's folate intakes and may already be providing adequate folic acid to prevent NTD [5]. In a recent analysis of reproductive-aged women (12–49 years) participating in NHANES 2007–2012, more than three-quarters had optimal RBC folate concentrations of ≥906 nmol/L. The mean RBC folate concentrations were higher among those women who reported taking supplements compared to those who did not; however, even among nonsupplement users, mean concentrations were >900 nmol/L [28].

Conclusions and Recommendations

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 [1]. 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. Given the (1) decreased absorption rates of high doses of folic acid, (2) concern of potential adverse health effects of high doses, and (3) the increased cost of supplements, it is time to reconsider the 4-mg dose recommendation.

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 factors associated with high risk of NTD [21]. 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. While clinical trials to reevaluate the dose of folic acid needed to prevent recurrent NTD in the era of food fortification would be ideal, they are unlikely to be performed. Thus, practitioners need guidance as to how to manage such patients today. Our review of the evidence suggests that is reasonable to use the much more readily available lower doses of folic acid.

Disclosure Statement

The authors report no conflicts of interest.

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