Folate: Its Biological Interactions and Strategies to Achieve Sufficiency Without Causing Excess

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"Prevention of neural tube defects (NTDs), congenital heart diseases (CHDs), facial clefts and other birth defects by folic acid (FA) supplementation" is an important milestone in the history of nutrition.[1(p1437)] The United States recommends FA for women of reproductive age to prevent 50% to 70% of neural tube defects.[2] The prevalence of neural tube defects is 1 to 10 per 1000 births, and food fortification and supplementation led to a decline of 10% to 80%, more with higher baseline prevalence.[3] However, FA supplementation may not reduce the prevalence to less than 0.5 of 1000 births. It is recommended that periconceptional FA supplementation start at least one month before pregnancy and continue throughout pregnancy. The dose recommended for high-risk mothers with an affected child for secondary prevention is 4.0 milligrams per day, and 0.4 milligrams per day is recommended for primary prevention.

The Boston Birth Cohort Study (1999–2014) assessed pre- and postconceptional FA intake among 7612 mothers—3829 Black, 2023 Hispanic, 865 White, and 895 others—and estimated serum folate in one third of them.[3] Less than 5% of mothers started before pregnancy. One third of mothers had lower and one fourth had higher serum folate levels. Compared with Whites, Hispanics had lower values. The Centers for Disease Control and Prevention National Health and Nutrition Examination Survey and National Pregnancy Risk Assessment Monitoring System data[3] showed major differences in serum FA levels among different racial/ethnic groups. Lower levels were noted among smokers and overweight and obese women.[3] Women of reproductive age, pregnant women, and those with malabsorption, alcohol usage, or single nucleotide genetic polymorphisms (SNPs) involving folate-metabolizing genes are prone to deficiency.

Data on the magnitude of sufficiency and deficiency of FA is not available. PubMed and the World Health Organization Vitamin and Mineral Nutrition Information System surveys concluded that more nationally representative data are needed. FA deficiency is attributable to low intake, increased demand, and altered metabolism. As nutrient–gene interaction is a modifiable risk factor, it is important to ensure sufficiency.[4] Thus, food fortification and supplementation may benefit a large subset of the at-risk population, especially in developing countries, which have a high burden of multiple deficiencies and birth defects in offspring.

FA is supplemented periconceptionally, during pregnancy, and in various conditions such as nutritional and hemolytic anemias. The tolerable upper limit is fixed at one milligram per day.[5] But many individuals consume higher doses, because only five milligrams tablets are available in some countries. A study from India reported high serum folate levels in children on FA supplementation for hemolytic anemia, which remained high even after reducing the dose from five to one milligram per day.[6] The potential dangers of excessive folate include cancer, asthma, developmental delay, and autism.[3]

SOURCES AND FUNCTIONS OF FOLIC ACID

Vegetables, fruits, nuts, beans, peas, seafood, eggs, dairy products, meat, liver, poultry, and grains are rich in folate. Folate is also synthesized by the gut microbiome. Total body folate is 15 to 30 milligrams—one half stored in the liver and the rest in blood and body tissues. Folate refers to naturally occurring pteroyl-monoglutamic-acid. Approximately 85% to 100% of supplemental FA, the oxidized synthetic compound, is bioavailable. The active form Tetra-hydrofolic-acid/Tetra-hydrofolate (FH4/THF) plays a definite role in one carbon

metabolism in the body, along with other B vitamins.

THE ROLE OF FOLIC ACID IN EMBRYOGENESIS

The role of folate in embryogenesis[4] and normal cell division makes it vital throughout gestation, unlike vitamin B12, which is not uniformly expressed throughout embryogenesis. Hence, vitamin B12–metabolizing genes exert mainly "moonlighting" functions.

Epidemiological and genetic studies highlight that FA prevents birth defects by the cellular methylation process, known as the "methylation hypothesis." Genetic modulation by external factors, without causing mutation, is called epigenetics. Thus, genes can be switched on and off to modify gene expression. Folate acts in two ways: via the methylation cycle and as an epigenetic factor.

FOLIC ACID'S INTERACTION WITH OTHER NUTRIENTS

The interaction of folate with other nutrients is crucial. FA and vitamin B12 are important for the formation and maturation of red and white blood cells. These are cofactors in several metabolic steps involving one carbon metabolism, DNA synthesis, stability, repair, conversion of homocysteine to methionine, 5-methyl tetrahydro folate (5-MTHF) to THF and production of *S*-adenosyl methionine (SAM), and the methylation, demethylation, remethylation processes (Figure 1). DNA modulation, like silencing of genes, by virtue of methylation is essential for the development and closure of the neural tube in the brain and spinal cord and other structures at the appropriate time. SNPs involving the methylene tetrahydrofolate reductase (MTHFR) gene results in deficiency of 5-MTHF, affecting methylation reactions in the body, which is important in a variety of body functions and gene expression. SNPs involving folate-metabolizing genes reduce the enzyme efficiency by 70%, with medical implications. Approximately 10% to 30% of the population has such SNPs. A study on children with congenital heart diseases and their mothers showed a four- to fivefold increase in related SNPs compared with the control mother–child dyads.[1]

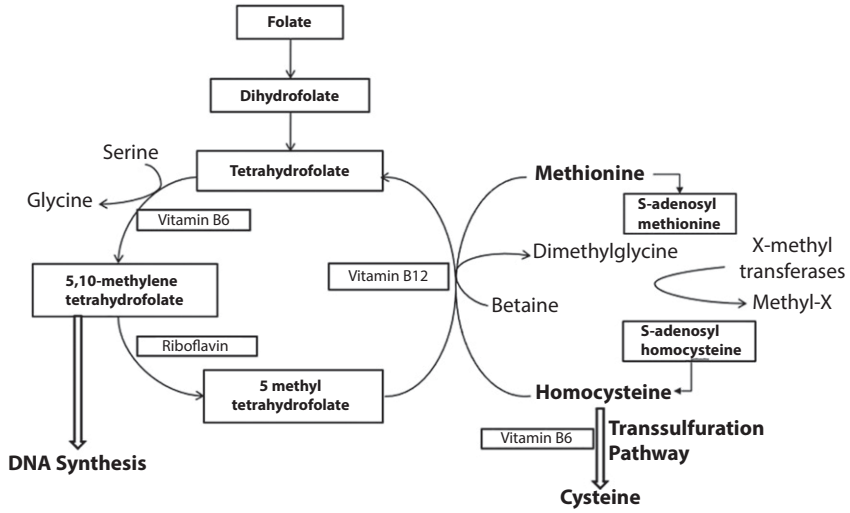

FIGURE 1— Metabolic Pathways and Functions of Folate and Vitamin B12

During folate transformation, a proportion of folate accidentally gets converted to the inactive metabolite 5-MTHF; this is known as the "methyl folate trap" and leads to a deficiency of 5,10-MTHF, which is essential for the synthesis of nucleic acids and DNA. In vitamin B12 deficiency, the methyl group cannot be transferred from methyl folate to the methionine cycle, so 5-MTHF accumulates. Thus, any folate from the diet is likely to get stuck in the inactive folate trap. This results in dyserythropoiesis, anemia, and cell damage. As the methionine cycle comes to a standstill (Figure 1), there is an increase in homocysteine, with multiple harmful effects in the body and a decrease in the SAM-dependent production of myelin, acetylcholine, and neurotransmitter synthesis.

Even though FA is a water-soluble vitamin, an excess can aggravate vitamin B12 deficiency by virtue of the folate trap. Vitamin B12 deficiency is rampant in strict vegans, those with malabsorption syndrome, those with absorption defects such as intrinsic factor deficiency, and other genetically susceptible individuals. Vitamin B12 deficiency leads to delayed milestones and neuroregression in infants, especially among offspring of deficient mothers, and juvenile pernicious anemia and spinal cord degeneration in older children and adults. Vitamin B12 is obtained from milk and milk products and nonvegetarian items. High folate with low vitamin B12 status during pregnancy is a risk factor for insulin resistance in the offspring.[7]

A study from South India reported FA, vitamin B12, and iron deficiencies as important public health problems, especially among 50% of women of reproductive age.[8] However, there are no universal supplementation and food fortification programs, except a targeted approach for iron and FA

supplementation. The supplementation recommendation is as follows: daily starting at 14 weeks of gestation through the first six months of lactation, biweekly from aged 6 to 60 months, weekly from aged 5 to 15 years, and among women of reproductive age. Standalone FA supplementation is given periconceptionally and whenever there is a medical reason.

REAPPRAISAL OF STRATEGIES

Many children and adults are on FA supplementation for different reasons. It is prudent to prevent FA excess, especially when there is possible vitamin B12 deficiency. Universal FA supplementation for all women of reproductive age without first establishing deficiency needs reappraisal—especially because most women are not planning a pregnancy. Nutrition education plays a key role in a healthy outcome with no deficiency or excess of the nutrient. Dietary diversity to ensure an adequate supply of all essential nutrients is the best strategy, as dietary sources are unlikely to cause excess vitamin consumption. FA supplementation, if undertaken, should be closely monitored, tailored on a weekly basis, and optimized to the tolerable upper limit.

SUMMARY

- Periodic surveillance is recommended to assess nutrient sufficiency and deficiency.
- Approaches such as dietary diversification and food fortification and supplementation should be adopted as needed and when feasible.
- Even though targeted FA supplementation to regulate gene expression is an exciting option, its interaction with other micronutrients and the possibility of excess FA must be considered. Ensuring enough other nutrients, especially vitamin B12, is important.
- A personalized rather than a one-size-fits-all approach is recommended to maximize health benefits and minimize adverse effects.
- Supplementation should not exceed the tolerable upper limit of 1000 micrograms per day and may be considered on a weekly basis, except for special therapeutic benefits. AJPH

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CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

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