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Beyond folic acid: can optimizing maternal status of other methyl donors contribute to further reducing the risk of NTD?

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Abbreviations: NTD, neural tube defects

In this issue of *The American Journal of Clinical Nutrition*, Petersen et al (1) present important findings from a multicentered, population-based, case-control study of >40,000 US pregnancies, suggesting that higher intakes of multiple micronutrients involved in one-carbon metabolism, individually or in combination, are associated with a reduced risk of neural tube defects (NTDs) in the offspring of women meeting current folic acid recommendations. NTDs are major congenital malformations of the central nervous system occurring as a result of failure in early pregnancy of the neural tube to close properly to form the brain and spinal cord, resulting in death of the fetus or newborn or lifelong disability. The most common forms of NTDs are anencephaly (a brain defect) and spina bifida (a spinal cord defect), depending on the portion of the neural tube that fails to close. Most children with NTDs who survive beyond birth will have serious lifelong disabilities. There are profound impacts for the individual, their families and society.

The finding of a beneficial effect of periconceptional folic acid supplementation of mothers in preventing NTD in their offspring ranks as one of the most important discoveries in human nutrition, and indeed in birth defects, research. Despite the availability of conclusive evidence for this effect for over 30 years (2, 3), the precise mechanism whereby folic acid (the synthetic vitamin form) protects against NTD remains to be fully elucidated. It must however involve one-carbon metabolism, a network of folate-dependent pathways requiring close interaction with other methyl donors. Thus, the latest finding by Petersen et al, suggesting that lower intakes of methyl donor nutrients apart from folate are implicated in NTD risk, is biologically plausible and consistent with certain previous reports, including an earlier study by the current authors (4, 5). In particular, there is considerable evidence showing that low maternal vitamin B12 status is an independent risk factor for having an NTD-affected pregnancy (6); likewise, lower amniotic fluid B12 concentrations and lower B12 binding capacity were reported in NTD-affected pregnancies (7).

One-carbon metabolism involves the transfer and utilization of one-carbon units (i.e methyl, formyl or formimino groups) in a network of reactions required for DNA and RNA biosynthesis, serine and glycine metabolism, histidine catabolism, methionine synthesis and methylation processes (8). For effective functioning of this network, folate needs to interact closely with vitamins B12, B6 and riboflavin. Reduced folates enter the one-carbon cycle as tetrahydrofolate (THF), which then acquires a carbon unit from serine in a vitamin B6-dependent reaction to form 5,10 methyleneTHF. Once formed, this folate co-factor is converted to 5 methylTHF, or serves as the one-carbon donor in the synthesis of nucleic acids, where it is required by thymidylate synthetase in the conversion of deoyxuridine to deoxythymidine for pyrimidine biosynthesis, or is converted to other folate co-factor forms required for purine biosynthesis. Methylenetetrahydrofolate reductase (MTHFR) is the riboflavin-dependent enzyme that catalyzes the reduction of 5,10 methyleneTHF to 5 methylTHF, the folate form used by methionine synthase for the vitamin B12-dependent conversion of homocysteine to methionine and the formation of THF. Methionine in turn is activated by ATP to form S-adenosylmethionine, the 'universal methyl donor' which donates its methyl group to more than 100 methyltransferases for a wide range of substrates such as DNA, hormones, proteins, neurotransmitters and membrane phospholipids (8). Thus, effective folate functioning requires essential metabolic interaction with vitamins B12, B6 and riboflavin, and therefore, inadequate intake of one or more of these B vitamins, or polymorphisms in folate genes, can impair one-carbon metabolism, even if folate intake is adequate (9-13). Given that other methyl donors play such critical roles in folate recycling, it is unsurprising, but not so widely reported, that their status would be important in preventing the range adverse health outcomes associated with impaired one-carbon metabolism including NTD. Petersen et al adds the most comprehensive evidence to date that optimizing maternal status of other methyl donors could contribute to further reducing the risk of NTD.

Petersen and co-authors set out to investigate whether intakes of the folate-related B vitamins B12, B6, riboflavin, and other methyl donors methionine, choline, betaine, along with thiamine, and zinc, individually or in combination, were associated with NTD risk reduction in offspring of women meeting the folic acid recommendations. Data were drawn from the National Birth Defects Prevention Study, a population-based, case-control cohort in the US, during the period 1999 and 2011. Cases (n=1227) were live births, stillbirths, or terminations affected by NTD. Controls were live births without a major birth defect (n=7095). Intakes of each micronutrient were categorized as 'higher' or 'lower' based on a combination of diet and periconceptional vitamin supplementation. The results show although that NTD associations with each individual micronutrient were weak to modest, much greater NTD reductions were observed with concurrent higher-level intakes of multiple micronutrients, with the strongest association - equating to ~75% lower NTD risk - observed with concurrent consumption of higher B6, B12, choline, betaine, and methionine, compared with intake of only one or no methyl donors in the higher range. The authors conclude that NTD prevention, in the context of folic acid fortification, could be augmented with intakes of methyl donors and other micronutrients involved in folate metabolism. The strengths of the Petersen study include its population-based design, the relatively large number of cases, the rigor of case classification, and adjustment for sociodemographic factors.

Despite this latest evidence suggesting benefits of other methyl donors, readers should note that the proven protective effect of periconceptional folic acid against NTD established over 30 years ago (2, 3) provides the evidence to support policy for women of reproductive age globally and has led to clear recommendations to take 0.4 mg/d folic acid before conceiving and in early pregnancy. But translating these recommendations into effective policy and practice has proved problematic over the years and, for huge proportions of women, we have not reached the stage where the primary goal of optimizing maternal folate status to prevent NTD has been achieved (14). On the one hand, in the US, along with 90 other countries worldwide, mandatory folic acid fortification has proven to be highly effective in optimizing folate status and reducing NTDs. In marked contrast, effective folic acid policy to prevent NTD has not been implemented in Ireland, the UK or other European country, and as a result, there has been no change in the incidence of NTDs over the 25-year period that the current strategy, recommending periconceptional folic acid supplements to women, has been in place. Concerns regarding potential adverse effects of folic acid have delayed the implementation of effective folic acid policy in Europe. Although the balance of available scientific evidence suggests that the proven benefits of mandatory folic acid fortification would more than outweigh any risks, folic acid is biologically highly potent, and dose remains an important consideration in any emerging policy, whether folic acid fortification or supplementation (15). Notably, recent studies from North America have addressed concerns regarding high-dose folic acid usage and concluded that higher-than-recommended folic acid doses are unwarranted for the prevention of first occurrence of NTDs (16). The implementation of mandatory fortification, wherever it is introduced, must therefore be accompanied by rigorous monitoring to ensure that the target folic acid levels for beneficial effects are reached, whilst avoiding any risk of overexposure at a population level.

The Petersen et al paper provides important new information with potential impacts for policy and practice in relation to NTD prevention. It provides convincing evidence that optimizing the status of methyl donors other than folate will have additional benefits in NTD prevention. As the authors point out, a randomized trial to confirm the roles of each of these nutrients in protecting against NTD is unlikely to ever be performed. In the absence of such conclusive evidence, it is important to recognize that the findings of the current paper, together with other lines of evidence, can make a meaningful contribution to emerging policy aimed at preventing NTD. Nonetheless, intervention with folic acid in early pregnancy remains the only proven measure to reduce NTDs and must remain the driver of evidence-based policy in the area globally. Thus, efforts worldwide should focus first and foremost on implementing mandatory folic acid fortification in the many countries worldwide (including throughout Europe) who have yet to introduce this effective measure and where current policy (educating women to take folic acid supplements) has proven to be ineffective in reducing NTDs for the past 25 years, and thus preventable NTDs are not being prevented. Urgent action is needed on implementation of mandatory food fortification with folic acid particularly in Ireland, where NTD rates are among the highest in the world, so that mothers and their babies can benefit.

Conflict of Interest Statement:

The author has no conflict of interest to declare

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