

Periconceptional Maternal Folic Acid Supplementation Mediate DNA Methylation Affecting Off spring Health

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Introduction

The maternal nutrient is extremely important for fetal development. Folate, VitB12, choline, betaine, methionine, etc, are essential methyl donors that play an important role during pregnancy. Folate is a critical factor in one-carbon metabolism which provides methyl groups for methylation [1]. There are various reports among the world suggesting that folate deficiency may induce neural tube disease (NTD), and maternal FA supplementation is recommended from 3 months before pregnancy to the first trimester of pregnancy. Therefore, the USFDA decided to carry out mandatory folic acid fortification in 1998. Consequently, the incidence of human NTD decreased by 35-50 % in North America. However, due to the implementation of the folic acid fortification in staple food, many women take in folic acid not only in the suggesting period but also in the second or third trimester. As a result, this has heated discussion about the consequences of FA supplements. A study suggested that maternal folic-acid supplement use is associated with changes in the DNA methylation of the offspring that persist for many years after exposure in utero [2]. Those aberrant methylations may be protection or inducement for childhood diseases, therefore, maternal folic acids supplementation is a double-edged sword. In this review, we address the epigenetic molecular mechanism of the diseases of offspring related to folate, including folate deficiency and the impact of maternal FA supplement in the different trimester.

Folate and one-carbon metabolism cycle

Folate, VitB12, choline, betaine and methionine both participate in the one-carbon metabolism (FOCM). Under the action of FOCM cycle enzymes, above-mentioned micronutrients convert to essential substrates for the following reactions of metabolic pathways. We eat folate and use the enzyme dihydrofolate reductase (DHFR) to convert into tetrahydrofolate (THF), which is the active form that carries one-carbon groups in a variety of reactions. Subsequently, with the action of serine-hydroxymethyltransferase (SHMT) and 5,10-methylenetetrahydrofolate reductase (MTHFR), THF transforms into 5,10-methylenetetrahydrofolate and finally convert to 5-methyl-THF. MTHFR serves a key role in one-carbon metabolism by converting methylene-THF to 5-methyl-THF. However, 5-methyl-THF on the one side serves as a transporter of the one-carbon unit participating in the purine and pyrimidine synthesis, which offer indispensable single carbon unit for nucleic acid synthesis. On another side, in the methionine synthase reaction, a methyl group is removed from 5-methyl-THF, which functions as a substrate, and is sequentially transferred to the vitamin B-12 coenzyme before homocysteine, thus forming methionine, to take part in DNA methylation and the synthesis of protein or phospholipid. All of the above reactions have an impact on cell growth, proliferation and differentiation, which are vital for the health of individuals.

Folic acid supplementation

Increase demand for nutrients during pregnancy, pregnant women require efficient methyl donors in order to meet maternal and fetal physiological needs for greater DNA synthesis and faster cell physical activities. Investigations into the therapeutic benefit of folic acid commenced in the 1930s, when Wills and colleagues investigated the treatment of tropical megaloblastic anemia with yeast and marmite and identified the presence of an unidentified bioactive factor [3]. Since then, scientists concentrated on to make use of folic acid to treat anemia, some ante-natal clinics recommended expectant mother to take in a prophylactic dose of folic acid for sake of folate deficiency-related anemia in Britain in the late [4-6]. Researchers didn't realize the efficacy of folate that could have a protective effect on neural tube disease until they pay attention to folate deficiency during pregnancy and prevalence of bearing abnormal infants in the 1960s [7-9]. In the past two decades after the first discovery that maternal folic acid supplements could reduce the NTD risk, various parts of the world recommended to add folate in dietary

of women who are pregnant, planning a pregnancy, and of childbearing age. In 2006, WHO approved the suggestion that women during childbearing age and those willing to have a baby should take in 400 µg folic acid every day to prevent NTD. Dietary reference values for folic acid intake during pregnancy vary internationally, with estimated daily average requirement values of 250 µg in the United Kingdom (UK); 370 µg in Japan; 400 µg in Europe; and 520 µg in Australia, United States (US), Canada and New Zealand [10]. These have been set using 5th to 95th percentile laboratory analyte values for red cell folate, for the first, second, and third trimesters of pregnancy, and are 137–589 ng/mL, 94–828 ng/mL, and 109–663 ng/mL, respectively (Daly, Kirke, Molloy, Weir, & Scott, 1995; Hursthouse, Gray, Miller, Rose, & Houghton, 2011). In 2015, WHO recommended that folate concentration maintain 960 nmol/L (400 ng/mL) in red blood cells of pregnant women during the early stages of pregnancy to prevent NTDs.

Conclusion

Therefore, maternal folate supplementation during pregnancy seems to be a double-edged sword to offspring health. Both beneficial and potential detrimental effects of maternal prenatal folate supplementation on offspring health should be considered. Although folic acid is essential for fetal development and NTD precaution, there is no known optimal level for folate. Further research on these issues will be forthcoming and important. On the one hand, it is urgent to do some experimental animal and in vitro researcher or retrospective analysis of offspring disease relating to FA supplement cases, which could be helpful for the most appropriate recommended dietary allowance for folate. Several studies are expecting to use autoantibodies as a treatment to interfere with folate transfer into the brain. Such treatments aiming at the FA-related disease should be developing and applying. On the other hand, FA supplement is clearly reducing the incidence of human NTD and other nervous system diseases which should not be overlooked and have a panic on folic acid intake.

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