Letter to Editor

Journal of Nutritional Biology

Balanced Essential Micronutrients during Pregnancy: High Concern

Srilatha B¹, Sailesh KS^{2*}, Aparna V³ and Rajagopalan V⁴

¹Department of Biochemistry, Apollo Institute of Medical Sciences and Research, India

²Department of Physiology, Vishu Dental College, India

³Department of Biochemistry, Mediciti Institute of Medical Sciences, India

⁴Director Research, Saveetha University, Poonamalle High Road, India

***Correspondence:** Sailesh K Sai, Department of Physiology, Vishu Dental College, Bhimavaram, India, Tel: 9061076459; E-mail: Saisailesh.kumar@gmail.com

Received date: July 09, 2018; Accepted date: October 09, 2018; Pub date: October 13, 2018

Introduction

Nutrition and epigenetic changes is the emerging topic of interest in the present scenario to understand the effects of increased supplementation of micronutrients like Folic Acid (FA). The study is taken up in the public health interest, to evaluate the importance of balancing the different micronutrients in the diet to avoid unbalanced nutritional disorders and other health complications later in life. It has been hypothesized that disease risks after birth or later in life can be determined by paternal or maternal diet. This raised an interest to study in-utero effects of environmental exposures like air pollution, toxins, nutrition, etc. It had been assumed that during embryonic period most of the dividing tissues get exposed to the environmental insults and that change results in predisposition of cancer or other health outcomes. There could be the possibility of maternal exposures like nutrition may alter the intrauterine one-carbon metabolism or the precursor milieu and may be involved in the disruption of one-carbon metabolism in developing offspring. Modification in methyl me of offspring with subsequent changes in phenotypes has been noted in the preliminary studies with increased folic acid (FA) supplementation during pregnancy. Maternal folate deficiency has been implicated as a cause of prematurity and both folate deficiency and cobalamin deficiency have been implicated in recurrent fetal loss and neural tube defects. Folic acid supplementation at the time of conception and in the first 12 weeks of pregnancy is expected to reduce by 70% the incidence of neural tube defects (NTDs) (meningomyelocele, encephalocele and spina bifida) in the fetus. Most of the protective effect can be achieved by taking folic acid, 0.4 mg daily at the time of conception. However there is no clear relationship between maternal folate status and the fetal abnormalities. It has been observed that, the lower the maternal folate, the greater the risk to the fetus. On the other hand maternal cobalamin status is a strong predictor of vitamin B12 in breastfed infants up to at least 6 months of age. Because of the transfer from mother to offspring during pregnancy and lactation, maternal requirements during this period are increased and deficiency may occur. The influence of low vitamin B12 during pregnancy may have cognitive ability of children later in life. Hypothyroidism is caused by insufficient production of thyroid hormones by the thyroid gland. In females, hypothyroidism is associated mainly with oligomenorrhea.

Thyroid dysfunction has also been linked to reduced fertility. Hypothyroidism has many effects on reproductive system development and functions. In women hypothyroidism is associated with delay in the onset of puberty, an ovulation, amenorrhea, hyper menorrhea, menstrual irregularities, infertility, and increased frequency of spontaneous abortions, premature birth, low-birth weight, fetal distress in labor, gestational hypertension, placental abruption, fetal growth retardation and impaired neuropsychological development of the offspring. Methyl group availability is

important for many cellular functions of neurons, including DNA methylation and gene expression control, nucleic acid synthesis and repair and protein metabolism. As a precaution folate supplementation has been recommended for pregnant women, as this simple intervention greatly reduces the incidence of neural tube defects in the offspring. Animal study has shown that excess supplementation of folate have suppressive effect on thyroid functions. High dose folate in women during pregnancy, decrease ion maternal plasma thyroid hormones may have significant implications for the health of the fetus. The ratio of folic acid and vitamin B12 that may play important role in determining global DNA methylation, as it was noted that excess maternal folic acid supplementation in the absence of vitamin B12 results in reduced global DNA methylation levels. Report suggests that an imbalance between folate and vitamin B12 during pregnancy could influence imprinting the embryo, perhaps by an effect on DNA methylation folate and co-substrates are required for biological methylation and nucleic acid synthesis. However it is not known whether excess folic acid might have any adverse effects on these functions. Evidence from in vivo studies has not clearly established a link between vitamin B12 and DNA methylation. In a study conducted by Fryer et al. [1] in the United Kingdom in the offspring of 24 pregnant women provided further support to explain the epigenetic consequences in the offspring as an effect of high folate supplementation in utero. They found a correlation between methylation of genomic lymphocytes and fetal birth weight and there was no association between maternal FA, cord blood folate and methylation of genomic lymphocytes. Further detailed study on methylation patterns of CpG (Cytosine and Guanine) dinucleotides showed significant association between plasma homocysteine concentration, lymphocyte methylation and infant birth weight [2]. Many studies stated that early life nutrition of the developing offspring accurately depends on maternal nutrition during pregnancy [3][4]. There is a correlation of maternal folate with cord blood and infant folate levels at 6 months of age. Wherein, umbilical cord blood folate levels are three times more than that in the mother. This scenario of increased exposure to dietary folate and circulating folate during pregnancy may lead to increased intrauterine folate environment and may have a significant impact on the growth, development and may also increase the risk for disease in the offspring. A study was carried out to estimate the status of folic acid and vitamin B12 in cord blood correlate and its association with maternal levels of thyroid hormones in third trimester of control, subclinical and overt hypothyroid pregnant women. The study states the importance of monitoring the levels of thyroid hormones in all the three trimesters. The prolong intake of folic acid alone may alter the ratio of folic acid and vitamin B12 causing the imbalance in the micronutrients. The positive correlation of the cord blood folic acid and vitamin B12 ratio with TSH may be due to the inhibitory effect of alter ratio of deiodinase enzyme on FT4 to get converted to FT3 which in turn may have the stimulatory effect on the synthesis of TSH. The study found inadequate literature in relation to the cord blood nutrients with thyroid hormones. To explore the knowledge in the field of nutrition and the detrimental effects of imbalanced intake of micronutrients had been an emerging topic of interest.

Currently many epigenetic studies in this context are taken up and are correlated with placental DNA methylation. The theory of changes in DNA methylation patterns in the developing offspring as a result of modulated environmental intrauterine exposure may include different levels of FA alone or may be the combination of various methyl donors is supported by many lines of evidences. Many studies stated that early life nutrition of the developing offspring accurately depends on maternal nutrition during pregnancy [5]. There is a correlation of maternal folate with cord blood and infant folate levels at 6 months of age. Wherein, umbilical cord blood folate levels are three times more than that in the mother. This scenario of increased exposure to dietary folate and circulating folate during pregnancy may lead to increased intrauterine folate environment and may have a significant impact on the growth, development and may also increase the risk for disease in the offspring. These epigenetic changes caused, may alter the gene expression and could be carried throughout the life span of an individual [5]. Imbalance in micronutrients might cause an epigenetic change in the mother as a result of altered ratio of folic acid/ vitamin B12 during pregnancy, further may be imprinted in the growing fetus and may be express later in life. A supplementary work done on placental DNA methylation with high folate and vitamin B12 levels in women during pregnancy found a correlation with ratio of cord blood folate and vitamin B12 with the placental DNA methylation of two genes Methyltetrahydrofolatereductase gene (MTHFR Gene) specific to folic acid and transcobalamin 2 (TCN2) to vitamin B12 showed methylation at promoter site. The methylation at the promoter region leads to the gene silencing. Certain studies suggest that the genotype, age, duration and magnitude of exposure should be considered as the response of global DNA methylation to the folate status is different at different conditions. In the above studies, a variation in DNA methylation was found between the sexes and ages [6] justifies the observations of different methylation patterns with low and high folate status.

Further mutation studies may give elaborative information about the patterns found in the study. Yet another animal study in sheep with maternal folate and vitamin B12 restricted diet resulted in aberrant methylation patterns i.e. only 4% of cytosine- guanine dinucleotide islands (CpG islands) out of 1400 CpG islands were methylated. Along with hypomethylation the adult male offspring also showed increased adiposity, altered immune function, high blood pressure and insulin resistance [7]. To explore the information regarding the DNA methylation effect on imprinting mechanism behind the suppression of FT3 and FT4 hormones.

Methylation depicts the quality of life in terms of diseased and health conditions. Proper development and function of placenta is crucial for the growth, health, and survival of developing fetus. Many studies had established links between epigenetic changes in the placenta and the risk of disease in gestation and early life [8]. Presently many studies on nutrition during pregnancy and placental outcomes are taken up to understand the basis of disease seen in early or later in life. Hence it is very important to maintain balanced essential micronutrients like folic acid and vitamin B12 during pregnancy as it has been proved that imbalanced nutrition during pregnancy may cause an epigenetic change in mother and may have an imprinting effect on the fetus or growing child that may be expressed later in life. Misregulation of epigenetic mechanism may have adverse effects on health and may lead to neurological disorders, developmental abnormalities and also cancer. Therefore, epigenetic modifications are evolving as very potent diagnostic and prognostic biomarkers in world of medicine.

References

1. Fryer AA, Nafee TM, Ismail KMK, Carroll WD, Emes RD, Farrell WE. LINE-1 DNA methylation is inversely correlated with cord plasma homocysteine in man: A preliminary study. *Epigenetics*. 2009;4(6):394-398. doi: <http://dx.doi.org/10.4161/epi.4.6.9766>
2. Fryer AA, Emes RD, Ismail KMK, et al. Quantitative, high-resolution epigenetic profiling of CpG loci identifies associations with cord blood plasma homocysteine and birth weight in humans. *Epigenetics*. 2011;6(1):86-94. doi: <http://dx.doi.org/10.4161/epi.6.1.13392>
3. Murphy MM. Maternal Homocysteine before Conception and throughout Pregnancy Predicts Fetal Homocysteine and Birth Weight. *Clin Chem*. 2004;50(8):1406-1412. doi: <http://dx.doi.org/10.1373/clinchem.2004.032904>
4. McKay JA, Waltham KJ, Williams EA, Mathers JC. Folate depletion during pregnancy and lactation reduces genomic DNA methylation in murine adult offspring. *Genes Nutr*. 2011;6(2):189-196. doi: <http://dx.doi.org/10.1007/s12263-010-0199-1>
5. Waterland RA. Early environmental effects on epigenetic regulation in humans. *Epigenetics*. 2009;4(8):523-525. doi: <http://dx.doi.org/10.4161/epi.4.8.10155>
6. Hajkova P, Erhardt S, Lane N, et al. Epigenetic reprogramming in mouse primordial germ cells. *Mech Dev*. 2002;117(1-2):15-23. doi: [http://dx.doi.org/10.1016/S0925-4773\(02\)00181-8](http://dx.doi.org/10.1016/S0925-4773(02)00181-8)
7. Sinclair KD, Allegrucci C, Singh R, et al. DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. *Proc Natl Acad Sci U S A*. 2007;104(49):19351-19356. doi: <http://dx.doi.org/10.1073/pnas.0707258104>
8. Kim J-M, Hong K, Lee JH, Lee S, Chang N. Effect of folate deficiency on placental DNA methylation in hyperhomocysteinemic rats. *J Nutr Biochem*. 2009;20(3):172-176. doi: <http://dx.doi.org/10.1016/j.jnutbio.2008.01.010>

Copyright: © **Srilatha et al.** This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.