One-Carbon Metabolism, Fetal Growth and Long-Term Consequences

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Methyl transfer or one-carbon metabolism is the key component of cellular metabolism, is involved in synthesis of purines, pyrimidines, and methylation of a number of substrates, proteins, DNA, RNA and indirectly, expression of a number of genes. The non-essential amino acid serine, folate and the essential amino acid methionine constitute the key components of methyl transfer. Since the methionine and folate cycles are ubiquitously present in every cell in the body and participate in key metabolic reactions, perturbation in their metabolism by nutrient deficiency, or by nutrient, hormonal and environmental interactions can have profound impact on the cell function, metabolism, growth and proliferation. Interest in the physiological changes in maternal-fetal and neonatal one-carbon metabolism, particularly in humans, has been primarily focused on the consequence of micronutrient deficiencies. In recent years with the recognition of the paradigm of developmental origin of health and disease and possibly epigenetic influences in programming of the phenotype, there has been a resurgence of interest in methyl transfer.

Data from studies in healthy pregnant women show unique adaptive responses in one-carbon metabolism of the mother [1]. These include a higher rate of transsulfuration in early gestation and a higher rate of transmethylation in late pregnancy. These are accompanied by a lower concentration of plasma homocysteine and changes in circulating levels of folate and B₁₂ and other methyl donors. Previous data in human fetus had documented the absence of hepatic transsulfuration due to lack of cystathionase (cystathionine-γ-lyase). A rapid appearance of transsulfuration occurs in the neonate immediately after birth. In the fetal sheep, a unique inter-organ cycling of serine and glycine, where glycine is taken up by the fetus from the placenta and converted to serine in the liver, has been demonstrated. This inter-organ cycling is accompanied by extremely high rates of glycine and serine flux in the fetus. These data may explain the high rates of transmethylation observed in the third trimester of human pregnancy.
Methionine metabolism is regulated by the nutrient and hormonal status of the organism. Three vitamins, folate, $B_{12}$ and pyridoxine are directly involved in the metabolism of methionine [2]. In addition, insulin and glucagon exert their effect directly by regulating the transsulfuration pathway or by effecting methionine synthase and indirectly by their effect on whole body protein turnover. Dietary protein restriction in animals also causes profound effects on one-carbon metabolism, causes an increase in serine biosynthesis, increase in transmethylation and decrease in activity of enzymes of transsulfuration cascade [3]. These effects are opposite to those due to folate and $B_{12}$ deficiency. In human, chronic protein malnutrition or lower protein intake in vegetarians has been associated with higher plasma homocysteine levels in a graded manner.

The impact of such nutrient insufficiencies or metabolic and endocrine perturbations on one-carbon metabolism in the mother and the growing conceptus has not been examined in humans. Based on the available physiological data, a profound influence can be speculated as evidenced by the demonstrated relationship between folate and $B_{12}$ insufficiency and metabolic programming [4]. Studies in animal models have shown that dietary protein restriction during pregnancy causes changes in maternal methionine homocysteine metabolism, impairs fetal growth, and results in metabolic reprogramming and long-term morbidity in the offspring [5]. Future studies using state-of-the-art (omics) technologies along with physiological and epidemiological cohort studies will address these critical questions and help develop intervention strategies at critical vulnerable periods during development.

References