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One carbon metabolism in pregnancy: Impact on maternal, fetal and neonatal health

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ABSTRACT

One carbon metabolism or methyl transfer, a crucial component of metabolism in all cells and tissues, supports the critical function of synthesis of purines, thymidylate and methylation via multiple methyl transferases driven by the ubiquitous methyl donor s-adenosylmethionine. Serine is the primary methyl donor to the one carbon pool. Intracellular folates and methionine metabolism are the critical components of one carbon transfer. Methionine metabolism requires vitamin B12, B6 as cofactors and is modulated by endocrine signals and is responsive to nutrient intake. Perturbations in one carbon transfer can have profound effects on cell proliferation, growth and function. Epidemiological studies in humans and experimental model have established a strong relationship between impaired fetal growth and the immediate and long term consequences to the health of the offspring. It is speculated that during development, maternal environmental and nutrient influences by their effects on one carbon transfer can impact the health of the mother, impair growth and reprogram metabolism of the fetus, and cause long term morbidity in the offspring. The potential for such effects is underscored by the unique responses in methionine metabolism in the human mother during pregnancy, the absence of transsulfuration activity in the fetus, ontogeny of methionine metabolism in the placenta and the unique metabolism of serine and glycine in the fetus. Dietary protein restriction in animals and marginal protein intake in humans causes characteristic changes in one carbon metabolism. The impact of perturbations in one carbon metabolism on the health of the mother during pregnancy, on fetal growth and the neonate are discussed and their possible mechanism explored.

1. Introduction

Pregnancy related clinical disorders such as eclampsia, spontaneous fetal loss, premature birth, birth defects, and fetal growth retardation are major contributors to perinatal morbidities worldwide. A large body of data exists in the literature relating a number of environmental, metabolic and endocrine signals to these morbidities. Amongst these, intrauterine growth retardation and small for gestational age is perhaps a major contributor both for its immediate effects on the neonate and for its relationship with the long term health of the offspring. Low birth weight, defined as weight less than 2500 gm at term gestation, a result of intrauterine growth restriction (IUGR) remains a critical public health problem in developing countries. For example, in India it represents almost 25–30% of all births and is a major contributor to perinatal and neonatal morbidity and mortality and to subsequent impaired growth and stunting (Sachdev, 2001). The impact of intrauterine growth retardation and consequent low birth weight on the long term health of the offspring has now been established in large epidemiological studies in humans from different parts of the world and shown in animal models (Barker et al., 1993; Hales, 1997; Yajnik et al., 1995; Godfrey, 1998; Ozanne and Hales, 2002; Whincup et al., 2008; Warner and Ozanne, 2010; Kalhan and Wilson-Costello, 2013). The relationship between fetal growth and its regulation and nutritional, and endocrine interactions between the mother, the placenta and the fetus has been studied extensively (Murphy et al., 2006; Fowden and Forhead, 2009). In relation to fetal mass, these studies have examined the regulation of nutrient (glucose, amino acids and fatty acids) transport across the placenta, their regulation and the direct contribution of these nutrients to fetal carbon accretion (Riskin-Mashiah et al., 2009; Higgins and Mc, 2010; Resnik, 2002; HAPO Study, 2009). However, certain amino acids, such as methionine, serine, glycine, not only

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contribute to protein mass, but also by their role in one carbon metabolism, play a unique role in the regulation of cellular metabolism, cell proliferation and may impact fetal growth. Methionine, an essential or indispensable amino acid and a component of all proteins, is also the *immediate* source of the methyl (one carbon) groups required for the methylation of nucleic acids, proteins, biogenic amines, and phospholipids (Brosnan and Brosnan, 2006). Methionine and folate are the key constituents of one carbon transfer, providing the one carbon units for the numerous methyl transferase reactions. Since the methionine and folate cycles are ubiquitously present in every cell in the body and participate in key metabolic reactions, in DNA synthesis and by methylation of DNA in gene expression, perturbation in their metabolism either by nutrient deficiency, or by nutrient, hormonal and environmental interactions can have profound impact on the cell function, metabolism, growth and proliferation. This may have its greatest impact on the growing embryo and the fetus. The purpose of this review is to present the physiological adaptations in one carbon metabolism in pregnancy, its perturbations by nutritional influences and the consequences to the mother and the neonate. Since the long term consequences of intrauterine growth restriction have been reviewed several times in recent years, the present review focuses on the effects of nutrition mediated perturbations in one carbon metabolism and their impact on the health of the mother and the newborn infant.

2. One carbon metabolism

One carbon transfer, a crucial component of cellular metabolism, is comprised of folate and methionine cycles and supports the critical function of the synthesis of thymidylate, purines and methyl transferase reactions. The methionine and folate cycles are ubiquitously present in eukaryote cells, and participate in key metabolic reactions, in DNA synthesis and via methylation reactions in the expression and regulation of numerous genes and their activity and may cause epigenetic changes. Nutritional, environmental, endocrine and other disruptions that can affect one carbon metabolism may result in profound change in cell function, metabolism, growth and proliferation. This may be most conspicuous during cellular growth and proliferation such as growing embryo, fetus and malignancy. A brief description of folate mediated one carbon transfer and of methionine metabolism follows. The reader is referred to outstanding scholarly reviews for details (Tibbetts and Appling, 2010; Christensen and MacKenzie, 2006; Stover and Field, 2011; Fox and Stover, 2008; Lu and Mato, 2012). The key features of one carbon metabolism are displayed in Fig. 1. As shown, the metabolism of folate and methionine are closely entwined and results in the transfer of methyl groups of serine and glycine for the numerous methyltransferase reactions. Methionine, an indispensable or essential amino acid is the immediate source of the methyl (one carbon units) groups required for the methylation of proteins, phospholipids, biogenic amines, nucleic acids and synthesis of creatine. The metabolism of methionine is composed of the ubiquitously present transmethylation cycle and the transsulfuration pathway. The transmethylation cycle involves the initial conversion of methionine and ATP into s-adenosylmethionine (SAM or AdoMet) catalyzed by methionine adenosyltransferase. SAM is the universal bioactive methyl donor and donates its methyl group to a large number of methyl acceptors catalyzed by methyltransferases. S-adenosylhomocysteine (SAH) is the byproduct of the methyltransferase reactions. SAH is reversibly cleaved into homocysteine and adenosine by SAH hydrolase. Homocysteine is remethylated to form methionine either by methionine synthase which requires vitamin B12 as a cofactor or by betaine homocysteine methyltransferase which uses betaine as the methyl donor. The methyl group for the remethylation of homocysteine by methionine synthase is donated by 5-methyl tetrahydrofolate (5 methyl THF), an intermediary in the folate cycle. Methionine is catabolized via transsulfuration cascade, present in the liver, pancreas, intestine, and kidney and possibly in the brain. Transsulfuration involves the transfer of sulfur (thiol) of homocysteine to serine to form cysteine and alpha ketobutyrate. The reactions are catalyzed by B6 dependent enzymes, cystathionine beta synthase and cystathionine gamma lyase. The carbon skeleton of homocysteine enters the TCA cycle as propionyl CoA formed by the decarboxylation of alpha ketobutyrate. Cysteine is the precursor of taurine as well as a component of glutathione. It is significant to note that the transsulfuration pathway is not active in the human fetus in utero and appears rapidly immediately after birth (reviewed by Kalhan and Bier, 2008; Kalhan and Marczewski, 2012). In addition to the requirement of B12, folate and B6 as cofactors, methionine metabolism is also effected by dietary protein intake (discussed below) and by the redox state. In addition insulin and glucagon modulate the metabolism of methionine by regulating the transsulfuration cascade, or by remethylation of homocysteine and indirectly by their effect on whole body turnover of proteins.

Intracellular metabolism of folate is compartmentalized between the cytoplasm and the organelles. (Tibbetts and Appling, 2010; Christensen and MacKenzie, 2006). Parallel cytosolic and mitochondrial pathways of folate mediated one carbon transfer and connected by one carbon donors serine and glycine have been described. It is postulated that serine, glycine and other methyl donors contribute to the mitochondrial one carbon pool of tetrahydrofolate (THF) to generate 5,10 methylene THF which is then oxidized by the mitochondria to formate and carbon dioxide and this formate is the source of methyl groups for the methylation of homocysteine in the cytoplasm. The expression of the mitochondrial metabolism varies in tissues during development and in other physiological and pathological states. The exact role of the interaction between mitochondrial and cytosolic one carbon transfer in human health and development remains to be identified.

2.1. Dietary protein and one carbon metabolism

Dietary protein restriction during pregnancy has been used extensively in rodents to examine the influence of maternal metabolic and nutritional environment on the immediate and long term health of the offspring. A number of outstanding studies have shown that dietary protein restriction early or late in pregnancy or during the lactation period causes fetal and neonatal growth restriction and predisposes the offspring to the development of obesity, type 2 diabetes and insulin resistance. The mechanism/s responsible for these long term consequences has not been delineated. In this context it is of interest that lower protein intake in both humans and animals has been shown to cause hyperhomocysteinemia and perturbations in one carbon metabolism. In the following section a brief discussion of these data are presented.

It is important to underscore the difference in metabolic and physiologic responses to isocaloric protein malnutrition and protein energy malnutrition. While the former is more often the consequence of lack of understanding of good nutrient habits and cultural constraints, the latter is the result primarily of poverty and economic adversity. Protein energy malnutrition results in responses that are similar to those of starvation i.e. increased gluconeogenesis, lipolysis, proteolysis, and negative nitrogen balance leading to loss of body (fat and protein) mass. A number of carefully done physiological studies have documented in detail the temporal metabolic responses to starvation in healthy and obese