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Maternal omega-3 fatty acids and micronutrients modulate fetal lipid metabolism: A review

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ABSTRACT

It is well established that alterations in the mother's diet or metabolism during pregnancy has long-term adverse effects on the lipid metabolism in the offspring. There is growing interest in the role of specific nutrients especially omega-3 fatty acids in the pathophysiology of lipid disorders. A series of studies carried out in humans and rodents in our department have consistently suggested a link between omega-3 fatty acids especially docosahexaenoic acid and micronutrients (vitamin B_{12} and folic acid) in the one carbon metabolic cycle and its effect on the fatty acid metabolism, hepatic transcription factors and DNA methylation patterns. However the association of maternal intake or metabolism of these nutrients with fetal lipid metabolism is relatively less explored. In this review, we provide insights into the role of maternal omega-3 fatty acids and vitamin B_{12} and their influence on fetal lipid metabolism through various mechanisms which influence phosphatidylethanolamine-N-methyltransferase activity, peroxisome proliferator activated receptor, adiponectin signaling pathway and epigenetic process like chromatin methylation. This will help understand the possible mechanisms involved in fetal lipid metabolism and may provide important clues for the prevention of lipid disorders in the offspring.

Contents

1. Introduction

Lipids and their derivatives are the major components of the body and are involved in many different functions. They are universally used for energy storage and thermal insulation in the body. Glycerophospholipids, sphingomyelin and sterols (mainly

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cholesterol) serve as the main structural components of biological membranes. Phosphatidylinositol serves as a reservoir of messenger molecules that are involved in signal transduction and molecular recognition processes [1].

Functional lipids such as the long chain polyunsaturated fatty acids (LCPUFA; omega-3 and omega-6 fatty acids) act as the precursors of prostaglandins and leukotrienes, which control blood clotting and arterial functions [2]. LCPUFA also regulate hepatic lipid metabolism and expression of genes involved in fatty acid synthesis and oxidation [3]. The metabolic effects of these fatty acids are reported to be mediated by peroxisome proliferator-activated receptors (PPARs), a key transcription factor responsible for lipid catabolism [4]. An earlier study in rodents demonstrated that dietary PUFA regulates hepatic lipid metabolism by enhancing the hepatic 5′ adenosine monophosphate-activated protein kinase activity (AMPK) and reducing the acetyl CoA carboxylase (ACC) phosphorylation and gene expression of carnitine palmitoyl transferase-1 (CPT1: regulatory enzyme in the fatty acid oxidation) [5].

It is well known that the dietary lipid intake during early pregnancy modulates lipid metabolism in the fetus [6]. Throughout pregnancy there are major changes in the maternal lipid metabolism to ensure a continuous supply of nutrients to the growing fetus [7]. Maternal lipid metabolism has shown to be associated with fetal lipids, fetal growth and fat mass [8]. Accumulation of fat in maternal depots is known to occur during early pregnancy and hyperlipidemia during late pregnancy. The lipolytic activity in the maternal adipose tissue increases during late pregnancy which plays a key role in the fetal development [9].

Studies have demonstrated that a nutritional stimulus occurring during critical periods of development leads to permanent changes in the offspring physiology which increases the risk of chronic diseases in adulthood [10]. Recent reports suggest that the metabolic set points of lipid metabolism are determined prenatally [11].

Evidence supports the notion that programming effects are a result of epigenetic changes [12,13]. Epigenetic modifications due to nutrient alterations is considered as a potential mechanism underlying fetal programming where key genes involved in lipid metabolism are more likely to alter during the early periods of development [14] and thereby influence lipid metabolic pathways in the offspring [15]. Vitamin B_{12} is a micronutrient that influences epigenetic changes [16] and affects the key genes involved in lipid metabolism [14]. Recent studies suggest that epigenetic mechanisms are also modulated by docosahexaenoic acid (DHA), a major omega-3 fatty acid with potential impact on the growth and development of the child [17]. However, the underlying mechanisms need to be established.

We hypothesise that alterations in the maternal intake or metabolism of both vitamin B_{12} and omega-3 fatty acids will influence fetal lipid metabolism (Fig. 1).

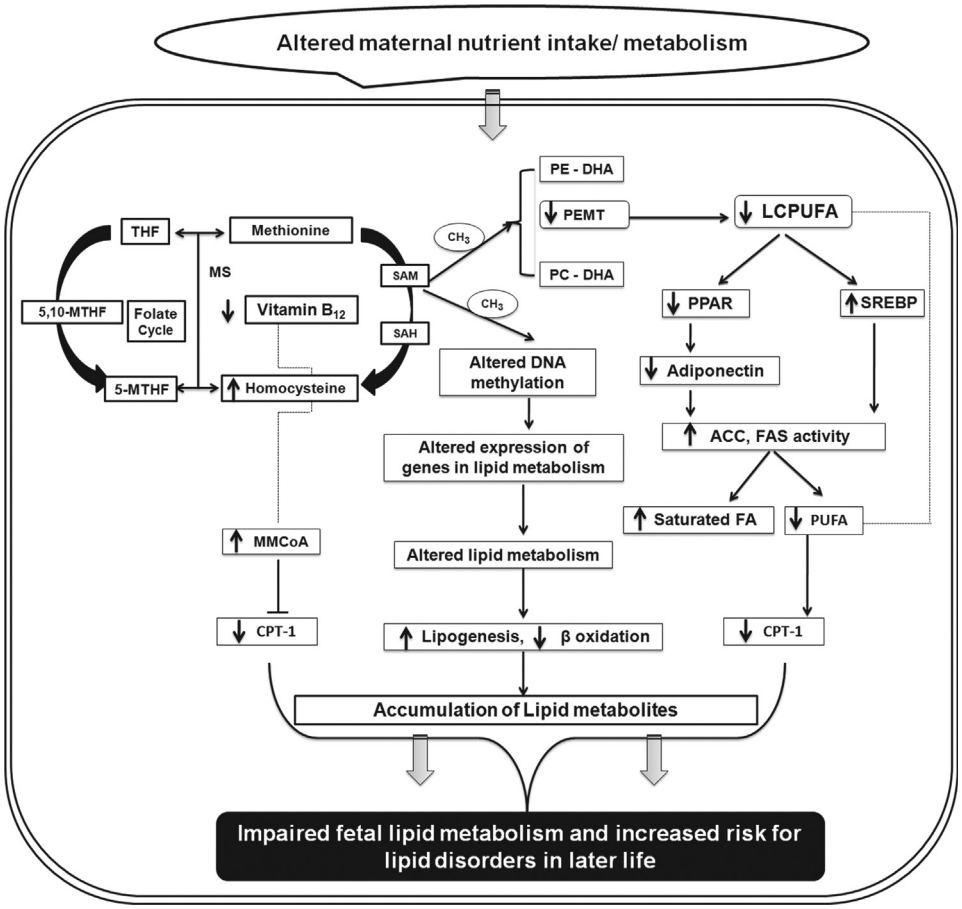

Fig. 1. The possible mechanisms through which altered intake/metabolism of omega-3 fatty acids and vitamin B_{12} affects fetal lipid metabolism. The figure provides the possible regulatory mechanistic pathways through which maternal omega-3 fatty acids and vitamin B_{12} influence the fetal lipid metabolism. Direction of the arrows up or down indicates the increase or decrease, respectively in the individual metabolic constituent. THF: tetrahydrofolate; 5,10-MTHF: 5,10-methylene tetrahydrofolate; 5-MTHF: 5-methylene tetrahydrofolate; MS: methionine synthase; SAM: S-adenosyl methionine; SAH: S-adenosyl homocysteine; MMCoA: methyl malonyl CoA; CPT1: carnitine palmitoyltransferase; CH_3 – methyl groups; PE-DHA phosphatidyl ethanolamine – docosahexanoic acid; PC-DHA phosphatidyl choline – docosahexanoic acid; PEMT – phosphatidylethanol amine-N-methyl transferase; LCPUFA: long chain polyunsaturated fatty acids; PPAR: peroxisome proliferator activated receptor; SREBP: sterol regulatory element-binding protein; ACC: acetyl CoA carboxylase, FAS: fatty acid synthase.