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Gestational Diet and Nutrition on Childhood Allergy and DNA methylation

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According to the World Allergy Organization (WAO), childhood allergy is a growing burden worldwide, with many of allergies begining in childhood or early adolescence. Asthma is included in the childhood "atopic march" model where development of atopic dermatitis begins early in life and is followed by onset of food allergies and then by allergic rhinitis and asthma. Asthma affects about 9% of children in the world and is one of the leading causes of absences from school [1]. Its frequency fluctuates from 1-30% among countries, being higher in westernized societies [1]. This increase is most likely multifactorial, with complex interactions of genetic, immunological and environmental factors, leading to the phenotypic expression of disease.

Environmental exposures during pregnancy can impact epigenetic mechanisms *In utero* and can cause epigenetic dysregulation that could lead to disease development [2]. One of the well-known epigenetic modification is DNA methylation that occurs within the one-carbon metabolism pathway. The addition of a methyl group along the DNA strand without changing the DNA sequence can affect the gene expression and has been shown to prevent coding and decrease the expression levels of the gene [3]. The developing fetus relies on the mother not only to deliver sufficient molecular precursors for organ development, but also to provide certain vitamins that modify immune programming.

Fish is a great source of n-3 long-chain polyunsaturated fatty acid (PUFA) and have anti-inflammatory properties and may reduce the risk of allergy [4]. Increased intake of marine n-PUFAs in the third trimester of pregnancy could have a protective role against asthma in the offspring [5]. The marine n-3 PUFAs, eicosahexaenoic acid and docosahexaenoic acid (DHA), leads to decreased availability of arachidonic acid and to increased competition for both the cyclooxygenase and lipoxygenase enzymes, resulting in decreased synthesis of arachidonic acid metabolites [4]. The risk of asthma has been shown to be lower in 7 year-old children if their mothers had high fish intake during pregnancy (≥2-3 times/week) compared to those mothers who never ate fish [6]. While some studies did not find any associations, maternal DHA supplementation across the second half of pregnancy had modest effects on child DNA methylation at specific regions of the genome [7].

Folate is another major nutrient required for tissue growth and fetal development during pregnancy. It provides the methyl precursor groups for DNA methylation and a decrease in

the level of dietary folate has been found to decrease DNA methylation [8]. Meta-analysis revealed impact of maternal folate (median weeks gestation=18 weeks and 12.9 weeks, respectively) in the developing epigenome [9]. Also, maternal folic acid supplementation during early pregnancy increased the risk of wheezing in early childhood [10]. The vitamin B_{12} is one of regulator of folate cycle, increases S-adenosyl methionine and results DNA hypermethylation. Maternal serum vitamin B_{12} showed inverse correlation with infant global methylation status [11].

Maternal total intake of vitamin K is directly associated with admitted asthma and current asthma at 7 years, and maternal intakes of vitamin A and E during pregnancy were weakly inversely associated with child allergic rhinitis [12]. Higher plasma levels of vitamin A was related to decreased DNA methylation in school-age children [13]. Risk of any allergic diseases such as wheezing, eczema and asthma can be reduced by higher maternal intake of vitamin C and higher consumption of copper, or both [14]. A study of prenatal supplement of vitamin D in the 2nd and 3rd trimester showed protective effect of offspring childhood asthma [15]. Also, vitamin D and E intake during pregnancy altered neonatal airway epithelial cell responsiveness and reduced risk of having doctor-diagnosed asthma at age 10 [16]. Maternal vitamin D intake during late stage of pregnancy and lactation altered DNA methylation in mothers and breastfed infants [17]. There is little research on iron intake during pregnancy and childhood wheezing and atopy. The only study suggests that reduced maternal iron status during first-trimester of pregnancy is adversely associated with childhood wheezing, lung function, and atopic sensitization during the first 10 years of life [18].

In conclusion, hypersensitivity early in life or even *In utero* may lead to numerous pathogenic conditions that are expressed later as diverse atopic reactions because of various factors such as environmental exposures, diet, and nutrient intake which directly or indirectly interacts with genetic factors. Not every food has an provocative or protective effect on the development of allergies, however certain dietary supplements containing n-3 fatty acids, vitamins A, C, D and E and iron may reduce lifetime risk of developing asthma. Nonetheless, the epigenetic mechanisms that lead to the development of allergies are not clearly understood and research is need to find connection between hypersensitivity and cellular responses. But some researchers studying atopy, myself including, suspect there is an poorly understood but influential role of methylation in developing allergic conditions.

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