The Future of Prenatal Nutrition

Using genetic testing to identify single nucleotide polymorphisms (SNPs) that create roadblocks in metabolic pathways to provide individualized nutrition to pregnant mothers for optimal fetal development

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Key Highlights

- Certain single nucleotide polymorphisms (SNPs) are common and can interfere with metabolism in a variety of nutrient metabolic pathways, leading to deficiencies that can impair fetal growth and development.

- The metabolic pathways involving choline, betaine (a metabolite of choline), methyl folate, B_{12}, and the essential fatty acid DHA play critical roles in pre-and postnatal cognitive development.[1]

- Prenatal genetic testing for SNPs affecting the metabolism of these nutrients allows for nutrition recommendations and supplementation tailored to each patient's genetic profile based on their algorithm.

- Examining multiple SNPs across related pathways, rather than one at a time, permits the development of a sophisticated algorithm that predicts whether a woman has genetically-caused roadblocks in metabolism, , and whether she is likely to repond to nutritional trteatments that bypass these roadblocks therby helping her to deliver optimal nutrition to her baby.

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[1] Steegers-Theunissen RPM, Twigt J, Pestinger V, Sinclair KD. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. Human Reproduction Update. 2013;19(6):640-655.

Introduction

Pregnancy is a unique window of opportunity for a mother to positively impact her child's growth and development through the nutrients she consumes. The choices a woman makes during this period of rapid growth can have significant consequences for her infant's cognitive function for years to come.

Current nutrition recommendations for pregnancy do not consider individual differences in the metabolism and transfer of nutrients to the fetus. This becomes especially important in the case of one-carbon nutrients such as folate, choline, betaine, and methionine, as well as for the essential fatty acid DHA. Each of these compounds plays a critical role in neurocognitive development, and the effects of maternal nutrition during pregnancy and breastfeeding can impact a child's brain function for at least 7 years after birth.

SNP Therapeutics' gene-guided nutrition test, developed using human clinical trials, accurately identifies 43 of the most common genetic inefficiencies and roadblocks in five metabolic pathways, each of which can affect pregnancy outcomes and fetal development. Using an algorithm based multiple genetic differences (single nucleotide polymorphisms; SNPs) in all these pathways, rather than on a single-gene variant provides the entire picture of how abnormalities in one nutrient pathway may affect another, allowing targeted medical nutrition therapy tailored to each patient's needs.

Women with one or more common genetic variants, called single nucleotide polymorphisms (SNPs), have higher needs for certain nutrients because their bodies do not efficiently metabolize them. While this can impact their own health, it is crucial to meet those increased needs during pregnancy to help prevent potentially devastating consequences for their offspring.

Consumer survey results showed that 97% of women would be very interested to know about genetic problems interfering with their ability to provide the nutrients needed for their child's cognitive development. By using the results of SNP Therapeutics precision nutrition genetic test and nutrition recommendations based on each woman's results, patients can make informed choices about their own health and that of their child.

Importance of One-Carbon Metabolic Pathways

One-carbon metabolism refers to an interrelated group of biologic pathways that use methyl donors such as choline, betaine (a metabolite of choline), methionine, and folate, as well as multiple cofactors including vitamins B_6 and B_{12}. These metabolic routes are essential for the

synthesis of proteins, cell membrane phospholipids, DNA and histone methylation, and for gene expression.[2,3]

Dysregulation in any of the one-carbon pathways during pregnancy can affect other pathways and result in neural tube defects, permanently impaired cognitive function, and abnormal physical growth.[4] Impairment may come in the form of inadequate dietary intake by the mother or SNPs that cause blockages in the metabolism and utilization of one-carbon nutrients.

Conversely, research shows that adequate and/or elevated intake of one-carbon nutrients in pregnancy results in improved cognitive skills in offspring and even a reversal of some effects of fetal alcohol exposure.[5] Studies from Harvard and Cornell universities, for example, indicate that optimal maternal intake of betaine, choline, folate, and B_{12} during pregnancy and lactation results in higher scores on tests of cognitive processing speed and visual memory in their offspring.

Choline

One of the prime methyl donors in the body is choline. Through its metabolite betaine, choline provides a methyl group in the conversion of homocysteine to methionine. Another of its main roles is in the production of phosphatidylcholine and sphingomyelin, major cell membrane phospholipids. Choline also contributes to the synthesis of the neurotransmitter acetylcholine.[6]

Along with folate, choline may be linked to the risk of neural tube defects and may enhance cognitive function, as indicated by studies showing improved cognitive test scores in children of mothers who had higher choline intakes during pregnancy.[7]

Choline is obtained from the diet (primarily animal sources such as liver and eggs) as well as from endogenous synthesis of phosphatidylcholine using the PEMT enzyme. Estrogen promotes activation of PEMT, increasing the body's ability to produce phosphatidylcholine. Biological requirements for choline increase in pregnancy and lactation due to the transport of large amounts ofthis nutrient from the mother to the fetus so as to sustain normal development. During pregnancy, elevated estrogen levels that activate the mothers ability to produce choline by activatig PEMT, allow the mother to meet the fetus's increased need for choline.[8] However, many women cannot fully activate PEMT. A 2010 study showed that up to 70% of women had a SNP in one copy of the PEMT gene and 19% had both copies of the gene affected, and these

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[2] Steegers-Theunissen RPM, et al. Human Reproduction Update. 2013.

[3] Zeisel SH, Niculescu MD. Perinatal choline influences brain structure and function. Nutr Rev. 2006 April; 64(4): 197-203.

[4] Korsmo HW, Jiang X. One carbon metabolism and early development: a diet-dependent destiny. Trends in Endocrinology & Metabolism. 2021;32(8):579-593.

[5] Zeisel SH, da Costa KA. Choline: an essential nutrient for public health. Nutr Rev. 2009;67(11):615-623.

[6] Zeisel SH, et al. Nutr Rev. 2006.

[7] Caudill MA, Obeid R, Derbyshire E, Bernhard W, Lapid K, Walker SJ, Zeisel SH. Building better babies: should choline supplementation be recommended for pregnant and lactating mothers? Literature overview and expert panel consensus. Eurn Gynecol and Obstet. 2020; 2(3):149-161.

[8] Zeisel SH, et al. Nutr Rev. 2006.

SNPs prevented estrogen from activating PEMT.[9] For these women, dietary 1-carbon nutriuents or diet supplements are much more important if they are to deliver enough of these critical nutrients to the baby

Although the Institute of Medicine has established an Adequate Intake (AI) for choline of 425 mg/d for females 19 years and older, 450 mg/d for pregnant women, and 550 mg/d for lactating women, many women may not be getting this amount, particularly during the critical times of pregnancy and lactation.[10] The reasons are twofold: most women don't find liver or eggs palatable during pregnancy, and a large percentage of women potentially have at least one SNP that interferes with choline metabolism and/or transfer to the fetus.

Betaine

Betaine is formed in an irreversible reaction from choline and contributes a methyl group in the conversion of homocysteine to methionine. Thus, betaine levels (and to a certain extent methionine levels) are dependent on the availability of choline.

Because of betaine's role in methionine synthesis from homocysteine, blood levels of homocysteine, a known risk factor for cardiovascular disease, can be lowered with betaine supplementation.[11]

Although there is no recommended daily intake for betaine, requirements are increased in the prenatal period just as they are for folate, choline, and other one-carbon nutrients. Nutrition sources include beets, broccoli, grains, shellfish, and wheat bran.

SNPs in the CHDH and BHMT genes can induce roadblocks in the metabolic pathways that include betaine, ultimately affecting DNA and histone synthesis.

Methionine

Methionine is an essential amino acid that is produced from homocysteine with a methyl group donation from either folate or betaine. It can be converted back into homocysteine through intermediary transformation to *S*-adenosylmethionine (SAM or AdoMet), which goes on to play a critical role in DNA and histone methylation.

Methionine is also a precursor to other amino acids, including cysteine, glutathione (which attenuates oxidative stress), and taurine using the cofactor vitamin B_6. In addition, methionine plays regulatory roles in digestion, lipid metabolism, and immune function.[12]

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[9] Fischer LM, da Costa KA, Kwock L, Galanko J, Zeisel SH. Dietary choline requirements of women: effects of estrogen and genetic variation. Am J Clin Nutr. 2010;92(5):1113-1119.

[10] Institute of Medicine, National Academy of Sciences Dietary reference intakes for folate, thiamin, riboflavin, niacin, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press, 1998:390-422.

[11] Olthof MR, van Vliet T, Boelsma E, Verhoef P. Low dose betaine supplementation leads to immediate and long term lowering of plasma homocysteine in healthy men and women. J Nutr. 2003;133(12):4135-4138.

[12] Martínez Y, Li X, Liu G, et al. The role of methionine on metabolism, oxidative stress, and diseases. Amino Acids. 2017;49(12):2091-2098.

Folate

Folate (vitamin B_9) functions as a methyl group donor to homocysteine in its transformation to methionine. As noted above, methionine is critical for DNA synthesis. Folate is well-known for its effects on neurocognitive development, and deficiencies in folate are associated with neural tube defects, including anencephaly and spina bifida.

Because of folate's integral role in central nervous system formation (particularly in the first trimester of pregnancy when a woman may not be aware that she is pregnant), the RDA for folate has been set at 400 mcg/day for all women of childbearing age.

Folic acid (used in food fortification and in vitamins) must be converted to several different forms of folate before it can be used in cell (e.g., methyl tetrahydrofolate for methylations, or formyl tetrahydrofolate for DNA synthesis). There are common SNPs in each of these pathways, and they can create metabolic roadblocks that limit the availability of the specific forms of folate that are needed. In addition, the SNPs discussed earlier that can block the use of betaine ans a methyl donor increase the demand for methyl tetrahydrofolate. Thus, in order to provide the best nutrion to their fetus, women with these SNPs need supplementation with a specific form of folate that genetically-caused roadblocks in their metabolism prevent them from making themselves.

Vitamin B_{12}

B_{12} is used as a cofactor in the conversion of homocysteine to methionine. SNPs affecting any of the other one-carbon pathways will also affect dietary requirements for B_{12} due to the need for B_{12} as a catalyst in the folate-mediated conversion of methionine to homocysteine.

Symptoms of One-Carbon Nutrient Deficiency

Due to the role of choline in the production of very low density lipoprotein (VLDL), which is needed for the transport of dietary fat and cholesterol from the liver to other tissues, a deficiency of choline results in fat accumulation in the liver. Adults who consume a 1-carbon-deficient diet exhibit steatosis (fatty liver) and muscle and liver damage, which can be reversible in some cases with choline supplementation.[13] Premenopausal women are somewhat protected from choline deficiency (barring any one-carbon SNPs in PEMT) due to estrogen's upregulation of the PEMT enzyme, which allows the body to make more endogenous choline when dietary intake is low.

During pregnancy, deficiencies in any of the one-carbon nutrients (either via low maternal dietary intake or SNPs) can have long-term effects on the infant in terms of cognition, DNA and

[13] da Costa KA, Kozyreva OG, Song J, Galanko JA, Fischer LM, Zeisel SH. Common genetic polymorphisms affect the human requirement for the nutrient choline. FASEB J. 2006;20(9):1336-1344.

histone methylation, and gene expression.[14] For instance, maternal choline and betaine deficiency are associated with a fourfold increase in neural tube defects.[15]

DHA: Essential for Cognitive Function

Docosahexaenoic acid (DHA), an omega-3 long-chain polyunsaturated fatty acid (LC-PUFA), is well-established in the literature as an essential nutrient that influences brain and eye development in the prenatal and neonatal periods.[16] DHA is carried into the brain as part of phosphatidylcholine-DHA in blood. Thus SNPs that affect the availability of choline and phosphatidykcholine as well as SNPs that affect the production of DHA itself, can create metabolic roadblocks that make it difficult for a pregnant mother to deliver adequate DHA to her fetus.

The accumulation of DHA in the brain takes place primarily in the last trimester of pregnancy and the first two years of life. It is largely dependent on maternal transfer through the placenta in pregnancy and breastfeeding after birth.[17]

One of the primary ways that DHA functions in cognition is through its role as an integral structural component in central nervous system membranes, although it is also involved in neuronal signaling, cell differentiation, and activation of gene transcription factors.[18]

Because the synthesis of DHA in the body is relatively low, dietary intake is responsible for providing adequate levels. The determination of those levels, however, is not straightforward. Research is now showing that, as with one-carbon nutrients, the extent to which DHA affects brain development may be influenced by gender and gene expression related to DNA synthesis.[19]

Both mother and child genetic variants appear to affect the extent to which DHA contributes to brain function. SNPs associated with LC-PUFA enzyme activity altered the amount of DHA in colostrum, children's performance on cognitive tests up to 4 years after birth, and the effect of breastfeeding on cognitive performance.[20]

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[14] Xu J, Sinclair KD, Xu J, Sinclair KD. One-carbon metabolism and epigenetic regulation of embryo development. Reprod Fertil Dev. 2015;27(4):667-676.

[15] Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. Am J Epidemiol. 2004;160(2):102-109.

[16] Sun GY, Simonyi A, Fritsche KL, et al. Docosahexaenoic acid (Dha): An essential nutrient and a nutraceutical for brain health and diseases. Prostaglandins Leukot Essent Fatty Acids. 2018;136:3-13.

[17] Carver JD, Benford VJ, Han B, Cantor AB. The relationship between age and the fatty acid composition of cerebral cortex and erythrocytes in human subjects. Brain Res Bull. 2001;56(2):79-85.

[18] Lauritzen L, Brambilla P, Mazzocchi A, Harsløf LBS, Ciappolino V, Agostoni C. DHA effects in brain development and function. Nutrients. 2016;8(1):6.

[19] Lauritzen L, et al. Nutrients. 2006.

[20] Morales E, Bustamante M, Gonzalez JR, et al. Genetic variants of the FADS gene cluster and ELOVL gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. PLoS One. 2011;6(2):e17181.

SNPs in the metabolic pathways involving DHA can have long-term effects on cognitive growth and development due to decreased DHA levels in pregnancy and lactation.

Why Test for SNPs in Pregnancy?

As discussed above, one-carbon nutrients and DHA play critical roles in normal fetal and neonatal development. Because many women have SNPs that affect their ability to provide adequate levels of these nutrients through placental and breastmilk transfer, they are at risk for negative pregnancy outcomes, and their children are at increased risk of lifelong negative physical and neurocognitive deficits.

Potential for Adverse Pregnancy Outcomes

One-carbon nutrients affect not only a mother's offspring but her own health as well. For example, elevated plasma homocysteine levels are associated with an increased risk of premature birth, very low birth weight, and preeclampsia.[21]

Impact on Childhood Development

Due to the far-reaching effects of one-carbon nutrients and DHA on the development of the brain and nervous system during the prenatal and neonatal periods, nutritional deficiencies can have lifelong consequences. Cognitive impairment in newborns and children is often associated with physical, educational, mental, and emotional problems.

SNP Algorithms vs. Single Genes

The pathways involved in one-carbon metabolism are complex and interrelated. Testing for aberrations in single genes does not take into account how one metabolic pathway is affected by inefficiencies in other pathways. By using proprietary algorithms, SNP Therapeutics has developed a system of identifying multiple gene SNP combinations that may alter an individual's absorption and utilization of each of the one-carbon nutrients and DHA needed for fetal development.

Considerations for Practice

Nutrigenetics is opening the way to tailored nutrition recommendations and supplementation based on each patient's specific genotype, contributing to improved outcomes for both mother and infant.

SNP Therapeutics precision nutrition reports provide a personal genetic profile score with low, medium, and high risk for nutritional deficiencies and abnormalities in each one-carbon

[21] Zeisel SH, da Costa KA. Choline: an essential nutrient for public health. Nutr Rev. 2009;67(11):615-623.

metabolic pathway tested. Detailed nutrition recommendations tailored to that patient's results are also included with optimal food sources for each nutrient.

By offering genetic testing during pregnancy, you will be able to give your patients individualized treatment plans to address any predispositions to blocked one-carbon and DHA metabolism and potentially avoid lifelong adverse outcomes for their children.