



# Is maternal diet supplementation beneficial? Optimal development of infant depends on mother's diet<sup>1-4</sup>

Steven H Zeisel

## ABSTRACT

There are periods during perinatal development in which specific nutrients are required for optimal development, and there is growing evidence that optimal dietary intake of these nutrients, which include iodine, docosahexaenoic acid, choline, and folate, is important. Lessons in how these nutrient effects were identified can help us to broaden our approaches for finding other critical nutrients: we are looking for nutrients for which there is a wide range of dietary intake, that have no or marginal pathways for biosynthesis, and that are needed by dividing progenitor cells. For some of the nutrients discussed, such as iodine and folate, the effects in humans are abundantly clear; for others, animal data are the most convincing. More human studies need to be conducted. We need a better understanding of diet and diet supplement intake during pregnancy and lactation and of whether diets are particularly low in some nutrients. Also, we need to understand how common genetic variations influence nutrient requirements during these periods. If we are going to supplement maternal and infant diets, first we must understand much more about the risks of having too much of a critical nutrient. Whatever the limitations of our current state of knowledge, it is apparent that pregnancy and lactation are periods during which good nutrition is exceptionally important. The infant is not protected from the inadequate diet of the mother. *Am J Clin Nutr* 2009;89(suppl):685S-7S.

## INTRODUCTION

The goal of the Experimental Biology Symposium on Maternal Supplementation (April 2008) was to review all available lines of evidence, delineate unanswered questions, and suggest a research agenda to determine whether maternal supplementation with specific nutrients might be beneficial. Nutrient requirements for the mother increase greatly during pregnancy, while at the same time fetal development is especially sensitive to the availability of some of these nutrients. Although we believed that the fetus was nourished adequately at the expense of maternal stores and needs, this series of articles in this supplement issue reviews evidence that this is not always true and that fetal development can be less than optimal if certain nutrients are not available during specific sensitive windows of development.

## IODINE

We have long recognized that iodine is one of the critical nutrients mentioned previously, and the article by Zimmerman (1) examined

current evidence supporting this conclusion. The iodine requirement during pregnancy is greatly increased because the mother synthesizes 50% more iodine-containing thyroid hormone, some of which is transferred to the fetus; in addition, the mother has increased renal losses of iodine (2). In areas of the world where seafood is not a common staple of the diet, maternal iodine deficiency can adversely affect cognitive development of the fetus and of children (decreasing IQ on average by a dozen points). Zimmerman (1) noted that it is unclear whether mild-to-moderate maternal iodine deficiency in humans produces more subtle changes in cognitive function, because there have been no controlled studies of long-term outcomes. There are many confounding factors that are difficult to separate from iodine deficiency, making assessments of the effects of modest iodine deficiency more difficult. The susceptible time window, during which dietary iodine is critical, is a relatively long one. Although providing adequate iodine in mid-to-late pregnancy improves infant cognitive development, there are greater benefits when iodine is given before or early in pregnancy (1). The most common strategy used to deliver iodine to pregnant mothers is universal salt iodization, but if access to iodized salt cannot be assured, the World Health Organization has suggested that diet supplements are appropriate (3).

## DOCOSAHEXAENOIC ACID

Docosahexaenoic acid (DHA, 22:6n-3) is one of a class of nutrients for which there is limited capacity for endogenous biosynthesis, and therefore it is conditionally required in the diet. Carlson (4) reviewed the evidence for maternal supplementation with this fatty acid. DHA is important during pregnancy and lactation because it is the major omega-3 (n-3) fatty acid needed

<sup>1</sup> From the Nutrition Research Institute, and the Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC.

<sup>2</sup> Presented at the symposium "Methyl Donors, Iodine, and DHA—Is Maternal Supplementation Beneficial?" held at Experimental Biology 2008, San Diego, CA, 6 April 2008.

<sup>3</sup> Supported by grants from the NIH (DK55865 and AG09525) and by grants from the NIH to the UNC Clinical Nutrition Research Unit (DK56350), the UNC General Clinical Research Center (RR00046), and the Center for Environmental Health and Susceptibility (ES10126).

<sup>4</sup> Reprints not available. Address correspondence to SH Zeisel, Nutrition Research Institute, Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, CB# 7461, Chapel Hill, NC 27599. E-mail: steven\_zeisel@unc.edu.

First published online December 30, 2008; doi: 10.3945/ajcn.2008.26811F.

to build fetal brain, and the rate of biosynthesis by elongation and desaturation of precursor fatty acids may be too slow to meet the requirement. It is interesting that single nucleotide polymorphisms (SNPs) in the genes coding for the fatty acid desaturases required for  $\Delta^5$  and  $\Delta^6$  desaturation of fatty acids are correlated with cognitive benefit derived from human milk (high in DHA content) compared with formula (lower in DHA) (5). Carlson noted that, although there are good data from animal models (6), there are few randomized trials in humans that show the benefits of maternal DHA supplementation during pregnancy or lactation for the child. However, Carlson reviewed multiple observational studies linking higher DHA intake by mothers with enhanced cognition or visual function in their children.

The susceptible window during which dietary DHA may be needed to optimize brain development is a relatively long one and extends from midpregnancy (7) into the first year of life (8). The most rapid rates of brain DHA accumulation in fetal brain occur during the last intrauterine trimester and the first year of life (4). Pregnant women are reducing their intake of DHA, especially in the United States, in part because of warnings about fish intake during pregnancy. This is reflected in lower breast-milk DHA concentrations; in US women, milk DHA concentration is <0.2% of total fatty acids, whereas in some Chinese women it is 2.8% of fatty acids (4). Two strategies could make more DHA available for brain development: maternal diet could include more fish and, where that is not possible, a supplement could be provided or infant formulas could be supplemented with DHA. In the last few years, many infant formulas have been modified to add DHA or other omega-3 fatty acids. Because we are not sure whether postnatal supplementation can correct fully for prenatal deficiency, it also seems appropriate to assure an adequate maternal intake throughout pregnancy and lactation.

#### CHOLINE AND FOLATE

Folate is an essential vitamin, whereas choline is another of the class of nutrients for which there is limited capacity for endogenous biosynthesis, and therefore it is conditionally required in the diet. Zeisel (9) examined the evidence that these nutrients are important for optimal brain development. Dietary folates, in the form of tetrahydrofolates, are essential cofactors for several biochemical reactions that transfer one-carbon units (10). Choline is required for membrane synthesis, methylation reactions, and for neurotransmitter synthesis (11). These nutrients are metabolically interrelated.

Dietary intake of folic acid can be marginal during pregnancy to the point that some pregnant women can become clinically folate deficient (12, 13). Dietary intake of choline has not been carefully described during pregnancy, but we know that the dietary requirement is influenced by several very common SNPs in genes of methyl metabolism (14, 15). Neural tube closure in humans is disrupted when either of these nutrients is not available during very early pregnancy (16, 17). In rodent models, both nutrients are also important later in pregnancy when the hippocampus develops; maternal dietary deficiency of either choline or folic acid diminishes neurogenesis and increases neural cell death in the fetal brain (18, 19). Rats that consume extra choline give birth to pups that perform better on memory tests, suggesting that this nutrient's effects on neurogenesis have functional significance (20). There are no equivalent studies in humans.

Two strategies could make more folate available for brain development: maternal diet could include more folate and folic acid and, where that is not possible, a supplement could be provided or infant formulas could be supplemented with folic acid. Rates of neural tube birth defects fell by 26% in the United States after enriched cereal grains consumed by women were fortified with 140  $\mu\text{g}$  of folic acid/100 g of grain (21). All prenatal vitamin supplements contain folic acid, as do infant vitamin supplements and infant formulas. Two strategies could make more choline available for brain development: maternal diet could include more foods such as eggs and liver and, where that is not possible, a supplement could be provided or infant formulas could be supplemented with choline. No prenatal vitamin supplements currently contain enough choline to adequately supplement a mother, but in the past few years many infant formulas have been modified to add choline. Because we are not sure whether postnatal supplementation can correct fully for prenatal deficiency, it seems appropriate to assure an adequate maternal intake throughout pregnancy and lactation.

#### USE OF DIETARY SUPPLEMENTS BY PREGNANT AND LACTATING WOMEN

Picciano and McGuire (22) reviewed diet supplement use in the United States and found a paucity of data concerning the use of dietary supplements during pregnancy and lactation. Although use of dietary supplements in the general US population is high and growing, demographic, sociologic, and economic factors influence supplement use. Female supplement users tended to be non-Hispanic white, more educated, and more affluent (23). Thus, individuals with perhaps the greatest risk for having inadequate diets were the least likely to take a supplement. Most pregnant women are advised to consume prenatal vitamin supplements. Picciano and McGuire found no consistent recommendations concerning dietary supplement use during lactation, although the American Thyroid Association recommends that breastfeeding women receive 150- $\mu\text{g}$  iodine supplements daily. The Institute of Medicine's most recent report (24) recommended that lactating women be encouraged to obtain their nutrients from a well-balanced, varied diet rather than from vitamin-mineral supplements. Whether recommended or not, Picciano and McGuire noted that the limited data available suggest that most pregnant women take supplements.

#### CONCLUSIONS

There is growing evidence that the fetus and young infant are not protected from the inadequate diets of their mothers. It appears that there are periods during development in which specific nutrients are required for optimal development. Scientists discovered the requirements for iodine, folate, choline, and DHA for optimal development because they thought to look at these specific components of the diet; there are likely to be many more critical nutrients when we cast a broader net in our research. Lessons in how these nutrient effects were identified can help us to broaden our approaches for finding more: we seem to be looking for nutrients for which there is a wide range of dietary intake, that have no or marginal pathways for biosynthesis, and that are needed by dividing progenitor cells.

For some of the nutrients discussed, such as iodine and folate, the effects in humans are abundantly clear; for others, animal data are the most convincing, with human data not yet at the state at which these



requirements should be engraved in stone. It is important that these human studies be conducted as randomized clinical trials because observational data are subject to confounding, especially when we are looking for subtle effects. However, while we wait for results from such studies, it might be costly to ignore these effects of nutrients and do nothing.

We have enough data on human diets during pregnancy and lactation to recognize that there is wide variation in nutrient intake, and it would be reasonable to attempt to move individuals with low intake up toward the population mean. It is becoming obvious that common genetic variations influence nutrient requirements. As our understanding of these SNPs is refined, we can identify women who appear to be consuming enough of a nutrient but who need to consume more because of a metabolic inefficiency. There may be many more nutrients that are conditionally essential during pregnancy and lactation. As noted in the series of articles from this symposium, such SNPs exist in pathways for the biosynthesis of DHA and of choline. There are millions of common SNPs and many of them must influence metabolism; it is important that we characterize these soon.

We need to consider the composition of prenatal supplements in light of such new data, just as we need to examine the composition of infant formulas used to substitute for breast milk. We do not know enough to describe all of the critically needed nutrients for optimal development, and although we remain relatively ignorant, we might use data on the mean dietary intake of populations and on the nutrient composition of human breast milk as approximations of the ideal until we know better. Already, we suspect that this approach can fail us; for example, maternal diets have changed over the last few decades such that breast milk in the United States is probably too low in DHA content to assure optimal development of the fetus.

If we are going to supplement maternal and infant diets, we need to understand much more about the risks of too much of a critical nutrient. It is possible that the same mechanisms responsible for nutrient effects on optimal development (eg, gene expression regulation by DNA methylation) can also result in unwanted side effects (eg, suppressing expression of a needed gene). Until we know more, it seems best to limit supplementation during pregnancy and lactation to levels that humans have had experience with—perhaps the upper quartile for population intake. In addition, we do not know the factors that influence compliance with diet supplement recommendations. At this time, we fortify the food supply with folic acid because we think that we cannot attain a level of compliance with supplement recommendations to adequately protect the population.

Whatever the limitations of our current state of knowledge, it is apparent that pregnancy and lactation are periods during which good nutrition is exceptionally important. The baby is not protected from the inadequate diet of the mother. We already know that a dollar invested in nourishing pregnant and lactating women results in a manyfold return in better infant outcomes. We are now uncovering some of the mechanisms responsible. While we are searching for specific supplements that optimize development, we should not forget to continue to invest in assuring that pregnant and lactating mothers have access to a good diet. (Other articles in this supplement to the Journal include references 1, 4, 9, 22, and 25).

The author has received funding from Balchem, from Mead Johnson Nutritionals, and from the Egg Nutrition Center. He serves on health advisory boards for Dupont, Solae, and Metabolon. None of these funds or activities influenced the content of this manuscript.

## REFERENCES

- Zimmermann MB. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr* 2009;89(suppl):668S–72S.
- Glinoeir D. The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. *Best Pract Res Clin Endocrinol Metab* 2004;18:133–52.
- WHO/UNICEF. Reaching optimal iodine nutrition in pregnant and lactating women and young children. Joint Statement of the World Health Organization and the United Nations Children's Fund. Geneva, Switzerland: World Health Organization, 2007.
- Carlson SE. Docosahexaenoic acid supplementation in pregnancy and lactation. *Am J Clin Nutr* 2009;89(suppl):678S–84S.
- Caspi A, Williams B, Kim-Cohen J, et al. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proc Natl Acad Sci USA* 2007;104:18860–5.
- McCann JC, Ames BN. Is docosahexaenoic acid, an n–3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *Am J Clin Nutr* 2005;82:281–95.
- Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n–3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* 2003;111:e39–44.
- Jensen CL, Voigt RG, Prager TC, et al. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. *Am J Clin Nutr* 2005;82:125–32.
- Zeisel SH. Importance of methyl donors during reproduction. *Am J Clin Nutr* 2009;89(suppl):673S–7S.
- Beaudin AE, Stover PJ. Folate-mediated one-carbon metabolism and neural tube defects: balancing genome synthesis and gene expression. *Birth Defects Res C Embryo Today* 2007;81:183–203.
- Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. *Annu Rev Nutr* 2006;26:229–50.
- Willoughby ML, Jewell FG. Folate status throughout pregnancy and in postpartum period. *Br Med J*. 1968;4:356–60.
- Qvist I, Abdulla M, Jagerstad M, Svensson S. Iron, zinc and folate status during pregnancy and two months after delivery. *Acta Obstet Gynecol Scand* 1986;65:15–22.
- 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;20:1336–44.
- Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. *Proc Natl Acad Sci USA* 2005;102:16025–30.
- Smithells RW, Sheppard S, Schorah CJ. Vitamin deficiencies and neural tube defects. *Arch Dis Child* 1976;51:944–50.
- 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;160:102–9.
- Craciunescu CN, Albright CD, Mar MH, Song J, Zeisel SH. Choline availability during embryonic development alters progenitor cell mitosis in developing mouse hippocampus. *J Nutr* 2003;133:3614–8.
- Craciunescu CN, Brown EC, Mar MH, Albright CD, Nadeau MR, Zeisel SH. Folic acid deficiency during late gestation decreases progenitor cell proliferation and increases apoptosis in fetal mouse brain. *J Nutr* 2004;134:162–6.
- Meck WH, Smith RA, Williams CL. Pre- and postnatal choline supplementation produces long-term facilitation of spatial memory. *Dev Psychobiol* 1988;21:339–53.
- Centers for Disease Prevention and Control. Spina bifida and anencephaly before and after folic acid mandate—United States, 1995–1996 and 1999–2000. *MMWR Morb Mortal Wkly* 2004;53:362–5.
- Picciano MF, McGuire MK. Use of dietary supplements by pregnant and lactating women in North America. *Am J Clin Nutr* 2009;89(suppl):663S–7S.
- Yu SM, Kogan MD, Huang ZJ. Vitamin-mineral supplement use among US women, 2000. *J Am Med Womens Assoc* 2003;58:157–64.
- Institute of Medicine. Dietary Reference Intakes: applications in dietary planning. A report of the Subcommittees on Interpretation and Uses of Dietary Reference Intakes. Washington, DC: National Academy Press, 2003.
- Greer FR. Introduction. *Am J Clin Nutr* 2009;89(suppl):661S–2S.

