SUPPLEMENT
OBG MANAGEMENT

Benefits of omega-3 fatty acids for fetal development persist through the lifespan

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The importance of 2 essential fatty acids (EFAs)—omega-3 and omega-6 fatty acids—for normal fetal growth and development has been well documented.[1,2] During pregnancy, the placenta transports EFAs from the mother to the fetus. The omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential for the development of brain, retinal, and other tissues.[3,4] These critical nutrients are derived solely through dietary intake. American diets are typically low in omega-3 fatty acids (found primarily in fish) but are sufficient in omega-6 fatty acids (in dairy products, meats, fried foods, and animal and vegetable oils). In the United States, pregnant and lactating women consume only 20% to 60% of the recommended omega-3 fatty acids. This maternal deficiency is likely to be compounded in the fetus.[5]

EFAS: EFFECTS ON PREGNANCY AND LABOR

Not only are EFAs structural building blocks for fetal cells and tissues, they also affect gestation and the birth process. Adequate maternal levels of dietary omega-3 fatty acids may increase birth weight, which is a strong predictor of an infant's subsequent health.[6,7] Essential fatty acids are precursors of agents that affect smooth-muscle relaxation, platelet activation, and inflammation. The omega-6 fatty acid arachidonic acid (AA) is converted by cyclooxygenase to prostacyclin, prostaglandins, and thromboxane A_2 (**FIGURE 1**),[8] which play various roles in pregnancy. Prostacyclin promotes uterine relaxation and fetal growth; prostaglandins initiate labor, and thromboxane results in postbirth hemostasis.

Timing of these actions is important: Premature activation of thromboxane could be a component of the pathophysiology of preeclampsia. Lipoxygenase products of AA (and other polyunsaturated fatty acids) inhibit prostacyclin production, which may decrease the prostacyclin:thromboxane ratio to a level that promotes vasospasm, smooth-muscle activity, platelet activation seen in preeclampsia, and other conditions in nonpregnant individuals.[2]

The omega-3 fatty acid EPA functions similarly to AA, with key differences: EPA cannot be converted to thromboxane. EPA can only promote a prostacyclin effect (through PGI_3) which effects vasodilation, decreases platelet activation and inflammation, and produces the smooth-muscle and vascular relaxation essential for blood flow to mother and fetus. These results prolong gestation. Further, it has been suggested that consumption of fish oil may normalize the prethrombotic state and reduce arterial disease in nonpregnant individuals.[9]

OMEGA-3 FATTY ACIDS: BENEFICIAL EFFECTS ON FETAL DEVELOPMENT

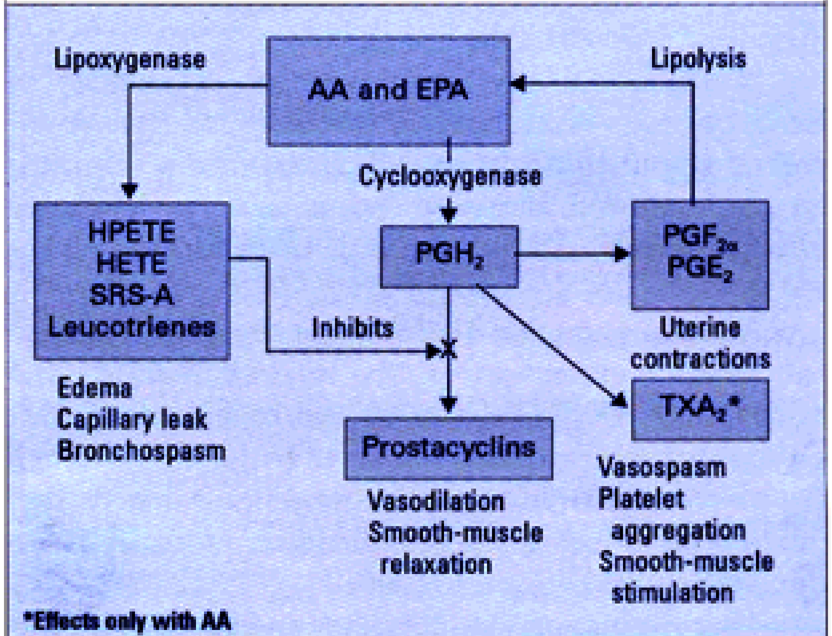
Clinical trials have demonstrated lower rates of low-birth-weight babies in cultures that consume high levels of omega-3 fatty acids compared with those that do not.[7] Dr Harris will review the effects of dietary or supplemental omega-3 fatty acids on length of gestation (**SEE PAGE 6**).

Essential for cognition and visual acuity

Docosahexaenoic acid plays both a compositional and functional role in visual and cognitive development: It makes up 40% of fatty acids in the brain and 60% of

FIGURE 1

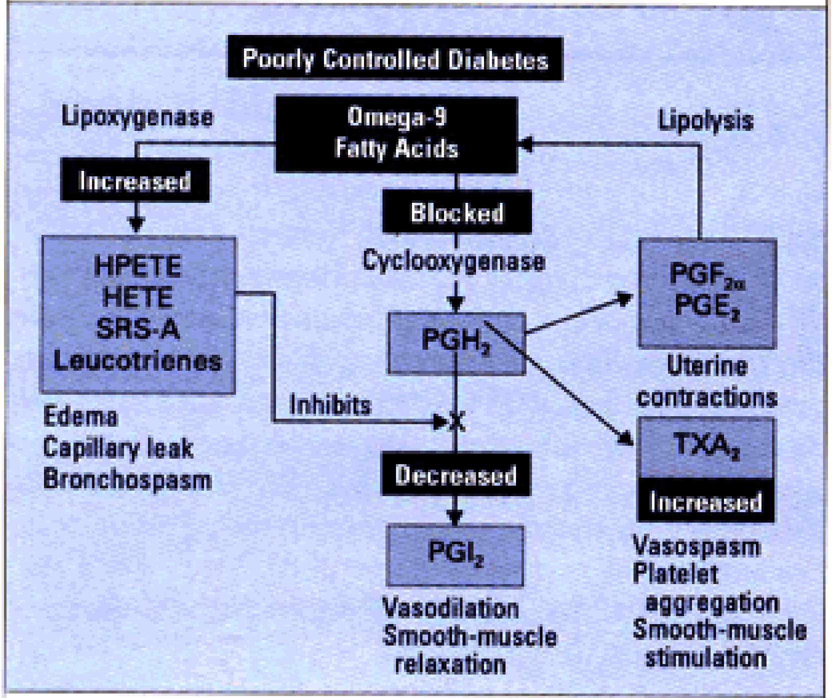
EFAs: Effects in pregnancy



AA = arachidonic acid; EFA = essential fatty acid; EPA = eicosapentaenoic acid; HETE = hydroxyeicosatetraenoic acid; HPETE = hydroperoxyeicosatetraenoic acid; PGE_2 = prostaglandin E_2; $PGF_{2\alpha}$ = prostaglandin F_2-alpha; PGH_2 = prostaglandin H_2; SRS-A = slow-reacting substance of anaphylaxis; TXA_2 = thromboxane A_2

FIGURE 2

Potential effects of poorly controlled diabetes on pregnancy



HETE = hydroxyeicosatetraenoic acid; HPETE = hydroperoxyeicosatetraenoic acid; PGE_2 = prostaglandin E_2; $PGF_{2\alpha}$ = prostaglandin F_2-alpha; PGH_2 = prostaglandin H_2; PGI_2 = prostaglandin I_2; SRS-A = slow-reacting substance of anaphylaxis; TXA_2 = thromboxane A_2

fatty acids in the retina. With the rapid development of the brain and nervous system in the third trimester, DHA transport from mother to fetus increases.[10]

Inadequate levels of DHA in the fetal retina and brain result in decreased visual function and learning deficits through numerous mechanisms.[11-13] Deficits in omega-3 fatty acids may affect the central nervous system during early development and increase vulnerability to depression. Deficiency has been shown to influence specific neurotransmitter systems, particularly the dopamine systems of the frontal cortex.[14,15]

In animal studies, imbalances or deficiencies of EFAs adversely affect the ability to respond to environmental stimulation. In one study, rats fed a saturated fat diet showed impaired water-maze performance along with less complex patterns of dendritic branching.[16]

A meta-regression-analysis revealed that a significant relation exists between the total DHA intake and visual acuity as reported in 14 controlled trials.[17] Fish oil supplements may also boost reading ability through improvement of the visual magnocellular system that theoretically mediates steady direction of visual attention and eye fixations on words.[18]

After evaluating the literature, an expert consensus workshop of the Child Health Foundation recommended a dietary supply of omega-3 fatty acids during pregnancy, lactation, and early childhood to avoid depletion of these essential nutrients.[19] It should be noted that during pregnancy the fetus receives adequate amounts of AA from the mother's diet, which typically contains an excess of omega-6 fatty acids, the source of AA.

EFAS AND HIGH-RISK PREGNANCIES

Metabolites of omega-6 fatty acids can have adverse effects (**FIGURE 1**). Abnormalities of thromboxane and prostacyclin physiology are associated with conditions such as preeclampsia, eclampsia, and pregnancy-induced hypertension,[3,20,21] further suggesting the importance of balance between omega-3 and omega-6 fatty acids.

Diabetes and hyperglycemia are associated with increased production of omega-9 fatty acid, a nonessential fatty acid produced by the body when levels of omega-3 and omega-6 fatty acids are inadequate. The 20 carbon omega-9 fatty acid, similar to AA and EPA, is called Mead's acid, a chemical that can be oxidized only by lipoxygenase. The excessive Mead's acid seen in diabetes may decrease prostacyclin production and lead to thrombotic and vascular injuries.

Thus, elevated omega-9 levels seen in diabetic pregnancy (**FIGURE 2**) may be linked to birth defects, preeclampsia, fetal hyperviscosity syndrome, and thrombosis.[4] Fetal macrosomia in diabetic pregnancy may be best prevented by good glycemic control; however, omega-3 fatty acids reduce plasma lipids and hyperglycemia, and may also help prevent and treat the metabolic abnormalities associated with diabetes.[22,23]

A consistent body of evidence has demonstrated that EPA and DHA reduce total mortality, cardiovascular mortality, and morbidity.[24] An animal study[25] showed that embryos that receive high levels of glucose have almost universal microvasculature injury and high rates of anterior body wall defects and spina bifida. It is important to note that addition of EFAs has been shown to be protective.

EFAS IN BREAST MILK

Some benefits of breastfeeding may be related to the levels of EFAs, which are higher in breast milk than in cow milk. The amount of DHA in human milk varies widely and is positively correlated with visual and language development in breast-fed infants.[11,12,26] Benefits of breast-feeding to the baby include more rapid development of motor skills and language, higher cognitive scores on testing, and lower risk for a variety of diseases. Benefits to the mother include decreased postpartum blood loss, lower risk of ovarian cancer and postmenopausal breast cancer, and better bonding with the child.[27,28]

Maternal supplementation increases the availability of omega-3 fatty acids in breast milk. As an alternative to breastfeeding, the US Food and Drug

Administration has approved the addition of EFAs (including omega-3 fatty acids) to infant formulas.

BEYOND PREGNANCY: EFFECTS ON NITRIC OXIDE

Research also suggests a possible link between folic acid and tetrahydrobiopterin, vitamin C, and polyunsaturated fatty acids in enhancing nitric oxide (NO) production. These effects may explain the beneficial actions of these nutrients in vascular conditions characterized by impaired endothelial NO response. A combination of these agents may form a novel approach to the prevention and management of conditions such as hyperlipidemia, coronary heart disease, atherosclerosis, peripheral vascular disease, and some neurodegenerative conditions.[29]

CONCLUSIONS

Omega-3 and omega-6 polyunsaturated long-chain fatty acids play key roles in health during the development of a fetus and, subsequently, throughout the lifespan. Studies have suggested that omega-3 fatty acids may also protect against a variety of diverse health conditions. Data have shown that patients with depression show depletion of red blood cell omega-3 fatty acids. Slower normalization of DHA status is associated with increased risk for symptoms of postpartum depression.[30,31] Assuring adequate levels of EFAs (including omega-3 fatty acids) before conception, during pregnancy and lactation, and throughout the lifespan, may represent a useful strategy to improve health and well-being. ■

REFERENCES

1. Burr GO, Burr MM. A new deficiency disease produced by the rigid exclusion of fat from the diet. *J Biol Chem.* 1929;82:345-367.
2. Ogburn PL Jr. Essential fatty acids and prostaglandins in pregnancy. In: Cowett RM, ed. *Principles of Perinatal Neonatal Metabolism.* 2nd ed. New York, NY: Springer Verlag; 1998:259-280.
3. Holman RT, Johnson SB, Ogburn PL. Deficiency of essential fatty acids and membrane fluidity during pregnancy and lactation. *Proc Natl Acad Sci USA.* 1991;88:4835-4839.
4. Schwarz K, Cox J, Savitri S, et al. Progressive decrease in plasma omega-3 and omega-6 fatty acids during pregnancy: Time course and effects of dietary fats antioxidant nutrients. *J Nutr Environ Med.* 1998;8:335-344.
5. Olsen SF. Further on the association between retarded foetal growth and adult cardiovascular disease. Could low intake or marine diets be a common cause? *J Clin Epidemiol.* 1994;47:565-569.
6. van Houwelingen AC, Sorensen JD, Hornstra G, et al. Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. *Br J Nutr.* 1995;74:723-731.
7. Olsen SF, Grandjean P, Weihe P, Videro T. Frequency of seafood intake in pregnancy as a determinant of birth weight: evidence for a dose dependent relationship. *J Epidemiol Community Health.* 1993;47:436-440.
8. Tapiero H, Ba GN, Couvreur P, Tew KD. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. *Biomed Pharmacother.* 2002;56:215-222.
9. Vanschoonbeek K, de Maat MP, Heemskerk JW. Fish oil consumption and reduction of arterial disease. *J Nutr.* 2003;133:657-660.
10. Green P, Yavin E. Mechanisms of docosahexaenoic acid accretion in the fetal brain. *J Neurosci Res.* 1998;52:129-136.
11. Innis SM. Perinatal biochemistry and physiology of long-chain polyunsaturated fatty acids. *J Pediatr.* 2003;143(suppl 4):S1-S8.
12. Gil A, Ramirez M, Gil M. Role of long-chain polyunsaturated fatty acids in infant nutrition. *Eur J Clin Nutr.* 2003;57(suppl 1):S31-S34.
13. Uauy R, Hoffman DR, Peirano P, Birch DG, Birch EE. Essential fatty acids in visual and brain development. *Lipids.* 2001;36:885-895.
14. Farquharson J, Jamieson EC, Abbasi KA, Patrick WJ, Logan RW, Cockburn F. Effect of diet on the fatty acid composition of the major phospholipids of infant cerebral cortex. *Arch Dis Child.* 1995;72:198-203.
15. Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res.* 1999;85:275-291.
16. Wainwright PE. Dietary essential fatty acids and brain function: a developmental perspective on mechanisms. *Proc Nutr Soc.* 2002;61:61-69.
17. Uauy R, Hoffman DR, Mena P, Llano A, Birch E. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *J Pediatr.* 2003;143(suppl):S17-S25.
18. Stein J. Visual motion sensitivity and reading. *Neuropsychologia.* 2003;41:1785-1793.
19. Larque E, Demmelmair H, Koletzko B. Perinatal supply and metabolism of long-chain polyunsaturated fatty acids: Importance for the early development of the nervous system. *Ann N Y Acad Sci.* 2002;967:299-310.
20. Otto SJ, Houwelingen AC, Antal M, et al. Maternal and neonatal essential fatty acid status in phospholipids: an international comparative study. *Eur J Clin Nutr.* 1997;51:232-242.
21. Min Y, Ghebremeskel K, Crawford MA, et al. Pregnancy reduces arachidonic and docosahexaenoic in plasma triacylglycerols of Korean women. *Int J Vitam Nutr Res.* 2000;70:70-75.
22. Friedberg CE, Janssen MJ, Heine RJ, Grobbee DE. Fish oil and glycemic control in diabetes. A meta-analysis. *Diabetes Care.* 1998;21:494-500.
23. Montori VM, Farmer A, Wollan PC, Dinneen SF. Fish oil supplementation in type 2 diabetes: a quantitative systematic review. *Diabetes Care.* 2000;23:1407-1415.
24. von Schacky C. The role of omega-3 fatty acids in cardiovascular disease. *Curr Atheroscler Rep.* 2003;5:139-145.
25. Pinter E, Reece EA, Ogburn PL. Fatty acid content of yolk sac and embryo in hyperglycemia-induced embryopathy and effect of arachidonic acid supplementation. *Am J Obstet Gynecol.* 1998;159:1484-1490.
26. Das UN. Long-chain polyunsaturated fatty acids in the growth and development of the brain and memory. *Nutrition.* 2003;19:62-65.
27. Vastergaard M, Obel C, Henriksen TB, Sorensen HT, Skajaa E, Ostergaard J. Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatr.* 1999;88:1327-1332.
28. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr.* 1999;70:525-535.
29. Das UN. Folic acid says NO to vascular diseases. *Nutrition.* 2003;19:686-692.
30. Otto SJ, de Groot RH, Hornstra G. Increased risk of postpartum depressive symptoms is associated with slower normalization after pregnancy of the functional docosahexaenoic acid status. *Prostaglandins Leukot Essent Fatty Acids.* 2003;69:237-243.
31. Mischoulon D, Fava M. Docosahexaenoic acid and omega-3 fatty acids in depression. *Psychiatr Clin North Am.* 2000;23:785-794.