The Long and Short of It: Long-Chain Fatty Acids and Long-term Outcomes for Premature Infants

Maria Makrides, PhD[a], Ronald E. Kleinman, MD[b]

[a]South Australian Health and Medical Research Institute, and the Women's and Children's Health Research Institute, Adelaide, Australia; and [b]Department of Pediatrics, Massachusetts General Hospital for Children, Harvard Medical School, Boston, Massachusetts

www.pediatrics.org/cgi/doi/10.1542/peds.2015-0813

DOI: 10.1542/peds.2015-0813

Accepted for publication Mar 5, 2015

Address correspondence to Maria Makrides, PhD, Women's and Children's Health Research Institute, Level 7 Clarence Rieger Building, Women's and Children's Hospital, 72 King William Rd, North Adelaide, SA 5006, Australia. E-mail: maria.makrides@health.sa.gov.au

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Makrides receives honoraria (payable to the Women's and Children's Health Research Institute) for scientific advisory board contributions to Fonterra, Nestlé Nutrition Institute, and Nutricia. Dr Kleinman has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: Dr Makrides is supported by an Australian National Health and Medical Research Council Principal Research Fellowship (APP 1061704).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page 972, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2014-4094.

Dietary supplementation with long-chain polyunsaturated fatty acids (LCPUFA) for preterm infants has been a matter of intense interest since the early 1990s. The initial clinical studies from that time period demonstrated that adding omega-3 LCPUFA (mainly from marine oils) to the infant formulas of the day resulted in improved visual and retinal outcomes for preterm infants fed the supplemented formulas compared with those fed nonsupplemented formulas.[1–3] Until that time, formulas intended for preterm infants were devoid of LCPUFA. These and other studies[4] were designed to provide formula-fed preterm infants a dietary exposure to LCPUFA similar to that of the human milk–fed preterm infant; that is, ~20 mg/kg per day or 0.2% to 0.3% of total fatty acids as docosahexaenoic acid (DHA), which represents the median daily intake of most infants in resource-rich countries. These trials showed that LCPUFA supplementation of preterm infant formulas was safe. They also reported on the efficacy of various short-term outcomes of neural maturity in some subgroups of infants.[1–5] These findings resulted in the universal supplementation of infant formulas for preterm infants by the year 2000. Thus, current neonatal feeding practices provide premature infants roughly the same dietary intake of LCPUFA regardless of whether they are fed their mother's milk, preterm infant formula, or a combination of both.

However, a re-examination of LCPUFA accumulation rates during the last trimester of pregnancy found that the DHA which would need to be supplied during the neonatal period (~60 mg/kg per day [>1% total fatty acids as DHA in milk feedings]) surpasses that delivered by current typical feeding practices (~20 mg/kg per day).[6] Only 2 randomized trials have attempted to meet the physiologic requirement of DHA in the context of randomized controlled trials.[7,8] Both trials provided human milk to the intervention group supplemented to a concentration of ~0.85% DHA, and they compared these infants with a control group fed human milk at the standard concentration of ~0.2% DHA. However, as a result of the supplementation practices in both trials, the full presumed daily requirement for DHA was not achieved until full enteral feeds were achieved and both also ceased supplementation either at discharge from the hospital or at term. Collectively, these trials reported enhanced visual acuity,[9] better problem-solving ability,[7] and less cognitive delay at 18 months' corrected age.[8] These latter outcomes were most pronounced in girls and in infants born weighing <1250 g.

In this issue of *Pediatrics*, Almass et al[10] report the 8-year follow-up of the trial originally published in 2008,[7] which included 129 infants with a birth weight <1500 g. Ninety-eight children (45 in the intervention group and 53 in the control group) participated in the 8-year follow-up trial that demonstrated no differences in cognitive function or brain macrostructure as assessed by using magnetic resonance imaging.[10] These

results may not be completely unexpected, as the study was limited by the sample size and the differential loss to follow-up between the groups. However, surprisingly similar results were demonstrated by the 7-year follow-up of the other reported trial, which included >600 children born <33 weeks' gestation.[11] It may be that both trials did not test a high enough DHA dose, that the short-term outcomes were not generalizable to the entire test population or did not accurately reflect cognitive status, that the intervention was not administered for long enough, or most likely, that any shorter term cognitive benefits were diluted by the different external and dietary environments that the children experienced in the intervening time.

The essential question raised by these well-designed and well-conducted, long-term randomized longitudinal trials is whether increasing the concentration of LCPUFA in human milk fed to premature infants is necessary or advantageous. Do the other factors in human milk that contribute to neural development compensate for the relatively lower amounts of LCPUFA compared with calculated requirements? At this time, in the absence of demonstrated long-term cognitive benefits, it will be up to individual clinicians to decide if the shorter term visual and developmental benefits of increasing LCPUFA in the feedings of preterm infants are compelling enough to once again shift feeding practices in neonatal units caring for premature infants.

REFERENCES

1. Uauy RD, Birch DG, Birch EE, Tyson JE, Hoffman DR. Effect of dietary omega-3 fatty acids on retinal function of very-low-birth-weight neonates. *Pediatr Res*. 1990;28(5):485–492
2. Birch DG, Birch EE, Hoffman DR, Uauy RD. Retinal development in very-low-birth-weight infants fed diets differing in omega-3 fatty acids. *Invest Ophthalmol Vis Sci*. 1992;33(8):2365–2376
3. Carlson SE, Werkman SH, Rhodes PG, Tolley EA. Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. *Am J Clin Nutr*. 1993;58(1):35–42
4. O'Connor DL, Hall R, Adamkin D, et al; Ross Preterm Lipid Study. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. *Pediatrics*. 2001; 108(2):359–371
5. Smithers LG, Gibson RA, McPhee A, Makrides M. Effect of long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment: a systematic review of randomized controlled trials. *Am J Clin Nutr*. 2008; 87(4):912–920
6. Lapillonne A, Jensen CL. Reevaluation of the DHA requirement for the premature infant. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81(2–3):143–150
7. Henriksen C, Haugholt K, Lindgren M, et al. Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid. *Pediatrics*. 2008;121(6): 1137–1145
8. Makrides M, Gibson RA, McPhee AJ, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. *JAMA*. 2009;301(2):175–182
9. Smithers LG, Gibson RA, McPhee A, Makrides M. Higher dose of docosahexaenoic acid in the neonatal period improves visual acuity of preterm infants: results of a randomized controlled trial. *Am J Clin Nutr*. 2008; 88(4):1049–1056
10. Almaas AN, Tamnes CK, Nakstad B, et al. Long-chain polyunsaturated fatty acids and cognition in VLBW infants at 8 years: an RCT. *Pediatrics*. 2015;135(6): 972–980
11. Collins CT, Gibson RA, Anderson PJ, et al. Neurodevelopmental outcomes at 7-years' corrected age in preterm infants who were fed high-dose docosahexaenoic acid to term equivalent: a follow-up of a randomised controlled trial. *BMJ Open*. 2015;5:e007314

The Long and Short of It: Long-Chain Fatty Acids and Long-term Outcomes for Premature Infants

Maria Makrides and Ronald E. Kleinman

Pediatrics 2015;135;1128
DOI: 10.1542/peds.2015-0813 originally published online May 18, 2015;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Long and Short of It: Long-Chain Fatty Acids and Long-term Outcomes for Premature Infants

Maria Makrides and Ronald E. Kleinman

Pediatrics 2015;135;1128
DOI: 10.1542/peds.2015-0813 originally published online May 18, 2015;