

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

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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 studies⁴ 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 al¹⁰ 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.

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