Fish-oil supplementation: the controversy continues

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The fetal brain accumulates n–3 long-chain polyunsaturated fatty acids (LCPUFAs), especially DHA, rapidly in the second half of pregnancy. Western diets have changed to a relatively high n–6:n–3 fatty acid ratio largely because of increased consumption of vegetable oils. Modern diets also provide less fish, the main source of DHA, than recommended in pregnancy. This may be of concern as higher intakes of fish and DHA during pregnancy have been associated with better child development. However, trials of supplementation of fish oil (FO) or DHA during pregnancy have been inconclusive. Gould et al. (1) performed a systematic review of randomized controlled trials (RCTs) of n–3 LCPUFAs during pregnancy with neurologic and visual development in offspring as outcomes. They included 11 RCTs of >5000 children. The daily dose of DHA ranged from 200 to 2200 mg. Most RCTs had <100 infants randomly assigned per group and were powered only to detect large differences and measured multiple outcomes. The largest RCT \( n = 2399\); the DOMInO (DHA to Optimize Mother Infant Outcome) trial, found no difference in the primary outcomes, neurodevelopment at 18 mo, or maternal depressive symptoms (2). The only positive effect reported in the meta-analysis was in cognitive outcome from 2 trials at 2–5 y. The authors concluded that the evidence did not conclusively refute or support supplementation during pregnancy for improving cognitive and visual outcomes of offspring.

Assessment of outcomes specific to the role of DHA in brain development may provide better evidence for FO/DHA supplementation. Attention and behavior have been associated specifically and mechanistically with DHA status. In this issue of the Journal, Catena et al. (3) report a detailed assessment of the attention system at 8.5 y in 136 children whose mothers were recruited to a 2 × 2 factorial placebo-controlled trial of FO or folate or both in the second half of pregnancy (Nutraceuticals for a Healthy Life project). The executive, alerting, and orientating functions of the attention system were assessed by using behavioral and electrophysiological recording and electromagnetic tomography of the brain. No convincing benefit was found with FO supplementation. Further, the authors speculate that adding FO to the folate supplementation may be detrimental because the advantage seen in executive function in the folate-supplemented group was reduced when FO was added. These findings are consistent with the DOMInO study, in which a larger sample of pregnant women received a higher dose (800 mg DHA), and no difference was reported in their children’s distractibility, working memory, and inhibitory control at 2 y (4). The DOMInO authors hypothesize that the developing fetal brain is protected from dietary perturbation during pregnancy because of maternal DHA stores, up-regulation of DHA synthesis, and preferential placental transfer of DHA.

Supplementation of preterm infants during the preterm period is equivalent in timing to supplementation of the fetus during the last 10–20 wk of pregnancy. Another article in this issue of the Journal, by Molloy et al. (5), presents the visual processing outcomes at 7 y in a subgroup of 104 children who were enrolled in the DINO (DHA for the Improvement of Neurodevelopmental Outcome in Preterm Infants) study (6). As in the study by Catena et al. (3), the outcomes were very specific to the function of DHA. In the DINO study, mothers were supplemented during lactation to provide DHA at approximately 1% of fatty acids in the breast milk (60 mg/d DHA) similar to the dose of DHA that the fetus would receive in utero. The control group received breast-milk concentrations of DHA (0.3%) or formula supplemented with 0.3% DHA. There was no benefit in visual processing with the additional DHA supplement. Previously, in another subgroup of the DINO study, improved visual acuity was documented at 4 mo (7), but this 8-y assessment demonstrates no lasting benefit to preterm infants’ vision of supplementing DHA above concentrations found in breast milk.

In contrast to the lack of evidence supporting FO supplementation during pregnancy for cognitive and visual outcomes, there may be a benefit for immune or inflammatory outcomes. The meta-analysis of prospective cohort studies and RCTs by Best and colleagues (8) in this issue of the Journal suggests a benefit of FO supplementation during the last 10–20 wk of pregnancy on the incidence of allergic disease in offspring. There are plausible data to support modulation of fetal immune development with FO/n–3 LCPUFA supplements. The review includes 10 observational studies and 5 RCTs (900–3700 mg n–3 LCPUFAs). Eight of 13 publications from observational studies found a protective relation between high fish or n–3 LCPUFA intake and allergic outcomes. Five of 7 publications from RCTs found

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1 Abbreviations used: DINO, DHA for the Improvement of Neurodevelopmental Outcome in Preterm Infants; DOMInO, DHA to Optimize Mother Infant Outcome; FO, fish oil; LCPUFA, long-chain PUFA; RCT, randomized controlled trial.

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a protective effect on allergy or sensitization at one or more assessment times.

The 3 articles on FO supplementation published in this edition of the Journal contribute to the controversy by providing evidence that the developing fetal and preterm brain does not benefit from DHA supplementation of healthy pregnant and breastfeeding women in Western countries. Detailed assessment of the attention and visual systems, the functions most commonly proposed to be vulnerable to DHA depletion, appear to be unaffected by FO supplementation. Dietary supply and metabolism of fatty acids during pregnancy and lactation appear adequate for neurodevelopment of their infants. However, the data published in this edition suggest that further research on the effects of FO/DHA supplementation during pregnancy on the fetal immune system and the incidence of childhood allergies is warranted.

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REFERENCES