The Journal of Nutrition
Editorial

See corresponding article on page 3483.

DHA and Cognitive Development

Susan E Carlson[1] and John Colombo[2]

[1]Department of Dietetics and Nutrition, University of Kansas Medical Center, Kansas City, KS, USA; and [2]Department of Psychology, University of Kansas, Lawrence, KS, USA

In this issue of the *Journal of Nutrition*, Nevins et al. (1) provide a systematic review of omega-3 fatty acid supplements consumed during pregnancy and lactation and child neurodevelopment. The authors concluded that there is "limited evidence" for a favorable effect of supplementation in pregnancy on cognitive outcomes, and "insufficient evidence" to evaluate other developmental outcomes. Their findings are based on 8 randomized controlled trials (RCTs) and 1 prospective cohort study. We agree with this assessment of the state of knowledge on the subject, as well as with the authors' comment that there is not any doubt that omega-3 fatty acids are important for brain development. What we hope to offer are some thoughts on why RCTs of omega-3 fatty acid supplementation in pregnancy might have led to the conclusion of limited evidence despite their importance in brain development.

First, more mothers are taking DHA during pregnancy. There have been dramatic changes in intake of the omega-3 fatty acid DHA in both women and infants since it was first realized that both pre- and postnatal DHA intake from diet was low in many, if not most pregnancies (2). DHA and the omega-6 fatty acid, arachidonic acid (ARA), both found in all human milk, were added to infant formulas around 2002 after a series of RCTs in term infants showed improved visual acuity with DHA and ARA supplementation (3). After 2002, infants in Western countries received DHA postnatally either from infant formula or from their own mother's milk. Then around 2010, prenatal supplements of DHA entered the market, typically at a dose of 200 mg/day. Although the penetrance of prenatal DHA supplementation is not known, we do know that there has been an increase in some populations. In our most recent trial, half of the women were consuming a DHA supplement and half of those were consuming a supplement with ≥200 mg of DHA per day (4). Indeed, in RCTs of DHA supplementation during pregnancy that we conducted in the years 2006–2010 (5) and 2016–2020 (4) baseline red blood cell phospholipid DHA (the indicator we use to assess DHA status) increased from 4.3% to 6.4% of total fatty acids, respectively.

Second, infants are receiving more DHA postnatally. It is important to point out that the RCTs of omega-3 fatty acid supplementation in pregnancy—with the exception of Helland et al. (6)—were initiated after 2002 (i.e., after the widespread introduction of DHA and ARA into infant formula). We find it plausible that the postnatal DHA received by offspring in these studies might have conferred benefits on cognitive development. DHA accumulates in the brain predominantly between birth and 2 years of age, not in utero. Perhaps the near-universal provision of DHA to infants in Western countries that began around 2002 when DHA was added to infant formula provides sufficient DHA for optimal early brain development. If intake of a nutrient is already adequate, then it would seem unlikely that an additional benefit would be derived from supplementation. Prior to the ready availability of prenatal DHA supplements in the United States, we conducted a postnatal study of DHA and ARA supplementation and child cognition (18 months to 6 years). We found benefits on several cognitive outcomes, including preschool measures of rule learning and implementation and verbal ability (7), that we did not find in children of mothers supplemented with 600 mg of DHA/day in a pregnancy study initiated 4 years later [Kansas University DHA Outcomes Study (KUDOS)] (8).

Third, we agree with Nevins et al. (1) that the baseline maternal omega-3 fatty acid status could well be a factor in their analysis. Although use of maternal DHA supplements has been increasing, differences in seafood intake among the countries where the RCTs were performed could well have influenced maternal status and, in turn, affected child cognitive outcomes. For both reasons, omega-3 fatty acid statuses should be measured in any ongoing or future RCTs that enroll women with a range of DHA statuses. DHA statuses should also be measured at study endpoints to determine compliance with the intervention.

Authors of the systematic review (1) rightly point out that populations with lower socioeconomic status (SES) are underrepresented among published RCTs. It is well known that children of mothers with higher SES are cognitively advantaged, which may attenuate any cognitive benefit of omega-3 fatty acid supplementation. Lower SES is also linked to lower compliance with the intervention. We offer findings from our KUDOS RCT as a cautionary tale of how compliance linked to SES can confound study findings (8). The KUDOS cohort encompassed a range of SES. In KUDOS, if maternal RBC phospholipid DHA increased during the study (compliance with the intervention), verbal and full-scale IQ scores at 5 and 6 years of age were statistically higher than if maternal DHA status did not increase (placebo or low compliance) (8). However, these effects were no longer significant after controlling for SES. In the end, we could not conclude whether the higher cognitive scores in children related to the improved maternal DHA status were due to compliance with capsule intake or to the higher SES statuses of women who were most compliant with the intervention. Moreover, we were left with an important unanswered question

Author disclosures: SEC and JC have conducted randomized controlled trials of DHA supplementation in pregnancy and infancy with support from the National Institute of Child Health and Human Development and industry. Both have received honorariums for speaking about DHA from industry partners that provide DHA or manufacture products with DHA.

Address correspondence to SEC (e-mail: scarlson@kumc.edu).

Abbreviations used: ARA, arachidonic acid; KUDOS, Kansas University DHA Outcomes Study; RCT, randomized controlled trial; SES, socioeconomic status.

First published online September 29, 2021; doi: https://doi.org/10.1093/jn/nxab299.

of whether children of lower SES women might have received a cognitive benefit if their mothers had been more compliant with consuming DHA during pregnancy.

Seafood may be superior to supplemental omega-3 fatty acids, because seafood not only provides omega-3 fatty acids but it is an excellent source of other nutrients that are critical for in utero brain development, such as vitamin A, iron, zinc, iodine, and selenium (9), which are inadequate in the diets of many pregnant women. A recent systematic review of the relationship between seafood consumption during pregnancy and child neurodevelopment concluded there was "moderate and consistent evidence" that consumption of commercially available seafood during pregnancy is associated with favorable offspring neurocognitive development (10). The conclusion was based on a review of 29 prospective cohort studies comprising 102,944 mother-child pairs (10). The Dietary Guidelines for Americans Scientific Advisory Committee 2020–2025 report concluded there was an association between maternal seafood intake during pregnancy and infant/child cognitive development (11).

Finally, we want to point out that there is a likely benefit of maternal omega-3 fatty acid supplementation, which is well established as a mediator or long-term cognitive development. Well-documented clinical benefits of maternal omega-3 fatty acid supplementation in pregnancy are reduced risks of early preterm birth (<34 weeks gestation) and preterm birth (<37 weeks gestation) (12). A 2017 Cochrane Review concluded there are reductions of 42% and 11%, respectively, and the review linked the strongest evidence to studies that provided between 500 and 1000 mg of DHA per day (12). A secondary outcome of both the Docosahexaenoic Acid to Optimize Mother Infant Outcomes (DOMInO) RCT (13) and the KUDOS RCT (5) was a lower incidence of early preterm births. Two large RCTs were conducted subsequently to determine whether DHA could reduce early preterm births. Both found fewer early preterm births among women with a low baseline DHA status assigned to 800 mg of DHA/day instead of a placebo (14) or to 1000 mg instead of 200 mg of DHA/day (4). Preterm birth is a well known and widely accepted predictor of suboptimal cognitive outcomes (15); the reduction of preterm births seen in RCTs of prenatal DHA supplementation has likely prevented cognitive and language delays at a societal scale.

Acknowledgments

The authors' responsibilities were as follows—both authors: wrote the commentary, are responsible for the final content, and read and approved the final manuscript.

References

1. Nevins JEH, Donovan SM, Snetselaar L, Dewey KG, Novotny R, Stang J, Taveras EM, Kleinman RE, Bailey RL, Raghavan R, et al. Omega-3 fatty acid dietary supplements consumed during pregnancy and lactation and child neurodevelopment: a systematic review. J Nutr 2021;151(11):3483–94.
2. Zhang Z, Fulgoni VL, III, Kris-Etherton PM, Mitmesser SA. Dietary intakes of EPA and DHA omega-3 fatty acids among US childbearing-age and pregnant women: an analysis of NHANES 2001–2014. Nutrients 2018;10(4):416.
3. Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. J Pediatr 2003;143(4): S17–25.
4. Carlson SE, Gajewski BJ, Valentine CJ, Kerling EH, Weiner CP, Cackovic M, Buhimschi CS, Rogers LK, Sands SA, Brown AR, et al. Higher dose docosahexaenoic acid supplementation during pregnancy and early preterm birth: a randomised, double-blind, adaptive-design superiority trial. EClinicalMedicine 2021;36:100905.
5. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, Georgieff MK, Markley LA, Kerling EH, Shaddy DJ. DHA supplementation and pregnancy outcomes, Am J Clin Nutr 2013;97(4):808–15.
6. Helland IB, Smith L, Saarem K, Saustad 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(1):e39–44.
7. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, Gustafson KM, Brez C. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr 2013;98(2):403–12.
8. Colombo J, Shaddy DJ, Gustafson K, Gajewski BJ, Thodosoff JM, Kerling E, Carlson SE. The Kansas University DHA Outcomes Study (KUDOS) clinical trial: long-term behavioral follow-up of the effects of prenatal DHA supplementation. Am J Clin Nutr 2019;109(5): 1380–92.
9. Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr 2007:85(2):614S–20S.
10. Hibbeln JR, Spiller P, Brenna JT, Golding J, Holub BJ, Harris WS, Kris-Etherton P, Lands B, Connor SL, Myers G, et al. Relationship between seafood consumption during pregnancy and childhood and neurocognitive development: two systematic reviews. Prostaglandins Leukot Essent Fatty Acids 2019;151:14–36.
11. Dietary Guidelines Advisory Committee. Scientific report of the 2020 Dietary Guidelines Advisory Committee: advisory report to the Secretary of Agriculture and the Secretary of Health and Human Services. In: U.S. Department of Agriculture, Agricultural Research Service, eds. Washington (DC): 2020.
12. Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. Cochrane Database of Systematic Reviews 2018;2018(11):11Cd003402.
13. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P; DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA 2010;304(15): 1675–83.
14. Simmonds LA, Sullivan TR, Skubisz M, Middleton PF, Best KP, Yelland LN, Quinlivan J, Zhou SJ, Liu G, McPhee AJ, et al. Omega-3 fatty acid supplementation in pregnancy-baseline omega-3 status and early preterm birth: exploratory analysis of a randomised controlled trial. BJOG 2020;127(8):975–81.
15. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288(6):728–37.