Editorial

Omega-3 (n-3) long-chain polyunsaturated fatty acids (LCPUFAs), including eicosahexaenoic acid (EPA) and docosahexaenoic acid (DHA), are dietary fats linked with health benefits along the life span of an individual. These include a role in anti-inflammatory processes, viscosity of cell membranes, fetal development, and healthy aging. Since DHA is a key component of all cell membranes and is abundant in the brain and retina, much of the work has been focused on the perinatal period and the first 1,000 days of life. Literature exists underscoring the critical significance of healthy growth and development in the first 1,000 days of life in relation to morbidity and mortality. Towards this end, this period of growth may also be critical to the development of the brain and neurocognitive outcome. For women and children, optimal intake of DHA and a proper healthy diet could improve overall human health as well as decrease morbidity and mortality from a variety of neonatal diseases. The sources of DHA in a human diet, its presence in human breast milk, as well as the high concentrations in the human eye and brain are outlined. Further, the importance of maintaining an appropriate concentration of DHA throughout pregnancy, lactation, and the first 1,000 days is discussed since insufficient supply of DHA can impact mental and visual development and performance.

In this issue of *Annals of Nutrition and Metabolism*, the importance of and current information about DHA and EPA are discussed in relation to pregnancy and pregnancy outcome as well as with regard to reducing the in-

cidence of premature birth and associated comorbidities. Further, possible benefits in term infants and the evidence supporting or refuting the need for DHA are also presented.

In the first article, Philip Calder elegantly discusses the rapid accumulation of DHA and arachidonic (AA) acids during the last trimester of pregnancy which corresponds to the period of rapid growth and brain development. DHA comprises as much as 30–50% of neuronal plasma membranes by weight. He also points out that DHA accumulation in organs other than the brain as well as the accumulation of the other LCPUFAs is important to consider when determining optimal requirements. Premature infants, although having the capacity to convert α -linoleic acid to DHA and EPA, cannot fulfill the requirement based on fetal accretion rates, and current nutritional management leads to an early DHA deficit. In turn, DHA depletion may lead to reduced visual function and cognitive performance which may be improved by DHA and AA supplementation. Dr. Calder also goes on to discuss the mechanisms of the actions of DHA and that DHA is a substrate for biosynthesis of bioactive mediators. Since a lower DHA content in the brain and eye is linked to poorer cognitive development and visual function, it is vital that pregnant and lactating women as well as infants consume sufficient preformed DHA to support brain and eye development and function. DHA affects cell and tissue physiology; the effects include alterations in membrane structure and function, cell signaling, and

lipid mediator production. In addition, DHA reduces inflammation, improves immune function, and through these effects may have positive effects including reducing the risk of insulin resistance, metabolic syndrome, hyperlipidemia, and cardiovascular disease.

Makrides and Best present the available evidence and discuss the relationship between prenatal n-3 LCPUFA supplementation during pregnancy and the incidence of preterm birth. The importance of this is the fact that preterm births account for almost 85% of all perinatal complications including death and that approximately 50% of all preterm births do not have clear causes and there are no effective primary prevention strategies to prevent preterm birth. They discuss epidemiological data and evidence from randomized clinical trials to support an effect of increased n-3 LCPUFA intake during pregnancy on the length of gestation. The authors again stress the fact that the prenatal period is a time for increased risk of n-3 LCPUFA deficiency and that the WHO recommends an intake of 300 mg/day of these fatty acids during pregnancy. However, women in many low-, middle-, and high-income countries do not achieve this amount with the exception of those living in coastal countries. While marine foods are rich sources of n-3 LCPUFA, warnings against consumption of certain marine species may have reduced overall fish intake and, therefore, LCPUFA intake. This may be associated with the increasing rate of preterm birth. The evidence to date consistently demonstrates that n-3 PUFA supplementation during pregnancy increases the mean duration of gestation and produces a significant reduction in preterm birth. The inconsistencies between epidemiological observations and randomized controlled trials may not be surprising since observational studies are likely based on lifetime exposure compared to a defined period of supplementation in randomized controlled trials.

Meldrum and Simmer underscore the placental transfer of these fatty acids during gestation and point out that diets being insufficient, particularly in Western nations during pregnancy and lactation, may be unable to meet the high demands of the fetus and that countries, which experience typically low levels of DHA within breast milk include the USA (0.2%), Canada (0.14%), and Australia (0.25%). They go on to discuss the associations between maternal DHA and neurodevelopment of the infant, maternal supplementation with LCPUFA and neurodevelopment of the infant, and supplementation during lactation and neurodevelopment. Lastly, supplementation of term infants either through infant formulas or direct supplementation and their effects on neurodevelopment are

discussed. The authors conclude that there is no definite evidence that DHA supplementation in pregnancy, lactation, or infancy improves the neurodevelopment of healthy term infants and stress the need for larger trials to identify maternal factors, infant gender, and the optimal dose for supplementation to provide certainty for future recommendations.

Finally, Lapillonne and Moltu discuss trials, which demonstrate that larger amounts of DHA than currently and routinely provided are associated with better neurological outcome. Studies in preterm infants indicate possible benefits for retinal and cognitive development as suggested by greater retinal sensitivity to photic stimulation, more mature visual acuity, and short-term global developmental outcomes at 6–18 months after DHA supplementation in preterm infants. The studies are confounded by the variability in study designs and the amounts of DHA supplementation, where in some studies the amounts were chosen to produce the same concentrations of DHA and AA as in term human milk, which would be lower than the in utero accretion rate. The early advantage in neurological outcome up to 2 years of life does not appear to persist into childhood. However, as these authors caution, ‘this does not mean that supplementing with adequate amounts of LCPUFA during the perinatal period is not necessary’. They also cite studies demonstrating the growing evidence that besides the effect on growth, n-3 PUFA supplementation may attenuate immune and anti-inflammatory responses, reducing many of the comorbidities observed in preterm infants.

In summary, the n-3 LCPUFAs and their role in health and disease continue to evolve. While existing evidence for their role in the entire spectrum of the first 1,000 days is conflicting, the importance of a healthy diet including optimal amounts of these fatty acids cannot be overemphasized. The varying amounts of supplemental LCPUFAs in clinical studies, varying clinical designs, and selection of subjects results in meta-analyses producing conflicting results. Observational studies, which may also underscore lifelong healthy habits, demonstrate positive benefits of LCPUFA. Future trials need to be targeted to define subgroups of populations which may incur the most benefits while we also seek epigenetic data demonstrating the multiple benefits of LCPUFA in the human diet to improve pregnancy outcomes, infant neurodevelopment, and long-term health consequences.

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Jatinder Bhatia and Maria Makrides