Role of Long-Chain Polyunsaturated Fatty Acids in Neurodevelopment and Growth

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Abstract

There has been intense interest in the role of the n-3 long-chain polyunsaturated fatty acid (LCPUFA) docosahexaenoic acid (DHA, 22:6n-3), in growth and development of infants. In 2009, there are at least twelve published randomized controlled trials (RCT) assessing the effects of LCPUFA supplementation of infant formula for preterm infants and seventeen RCTs involving formula-fed term infants. In addition, at least five RCTs have investigated the effect of DHA supplementation during pregnancy and/or lactation on infant and early child development. Collectively, the published literature has demonstrated no harm of dietary LCPUFA for infants regardless of whether they are born preterm or at term. However, developmental benefit is more consistently observed in infants born preterm. This may be explained by the fact that DHA accretion to neural tissues peaks during the fetal brain growth spurt in the last trimester of pregnancy. Infants born preterm are denied the full gestation period to accumulate DHA and are at risk of incomplete DHA accumulation. New research is focused on the timing and dose of DHA supplementation needed to optimize developmental outcomes.

The synaptosomal membranes of the central nervous system contain high concentrations of the n-3 long-chain polyunsaturated fatty acid (LCPUFA) docosahexaenoic acid (DHA)(22:6 n-3). Animal studies show that diets deficient in n-3 fatty acids are associated with reductions in brain DHA concentrations, decreased dopamine and serotonin, reduced neuronal cell size as well as decreased visual function, impaired visual recognition memory, and compromised learning behavior [1]. The first publication in human infants, which was based on the findings from primate studies was in 1990. It reported that preterm infants fed a formula supplemented with n-3 LCPUFA, mainly
as DHA, had improved retinal sensitivity compared with preterm infants fed the standard unsupplemented formula of the day, which were low in n-3 fatty acids and rich in n-6 fatty acids [2]. Since then, there has been an explosion of interest in the role of LCPUFA in growth and development of all infants. In 2009, there are at least twelve published randomized controlled trials (RCTs) assessing the effects of LCPUFA supplementation of infant formula for preterm infants and seventeen RCTs involving formula-fed term infants. In addition, at least five RCTs have investigated the effect of increasing the DHA concentration of human milk through maternal supplementation on indices of infant and early child development and several are actively investigating the effects of DHA supplementation during pregnancy. This degree of research activity has resulted in a wealth of quality information regarding the effects of LCPUFA on infant growth and development. Collectively the published literature has been free of reports of harm from dietary LCPUFA for infants, although the consistency of benefit has been lacking. Some trials report positive effects of LCPUFA supplementation at multiple time points, others report positive effects at some ages but not others, while some report no effects at all. The scope of this paper is to review whether the effects of LCPUFA are influenced by the type of LCPUFA used in dietary supplementation, the timing and the dose of supplementation.

**Type of LCPUFA Supplementation**

The animal and mechanistic work all point to the functionality of DHA in neurodevelopment, but it is rare that DHA is the only added LCPUFA. The initial trials with infants involved testing the effects of fish oil-supplemented infant formulas on aspects of visual development. These trials used MaxEPA type fish oil where the concentration of eicosapentaenoic acid (20:5n-3) was higher than DHA. Although these early trials showed that fish oil supplementation of infant formula improved visual development during infancy [3, 4], some observed poorer growth when preterm infants were fed formulas containing only n-3 LCPUFA that resulted in a depression of plasma arachidonic acid (AA, 20:4n-6) [5]. It was hypothesized that n-3 LCPUFA supplementation may have been a factor contributing to the growth deficit. However, this hypothesis has not been substantiated by systematic reviews of RCTs of LCPUFA supplementation [6, 7]. In term infants, we identified fourteen eligible trials that had data available for meta-analysis (1,846 infants) and the analysis showed no positive or negative effect of LCPUFA supplementation on infant weight, length or head circumference at any assessment age [6]. Importantly, subgroup analyses showed that supplementation with only n-3 LCPUFA (no AA) had no effect on infant weight, length or head circumference despite reductions in the plasma and erythrocyte AA status of infants involved in these trials
[6]. Similarly, systematic reviews of trials involving preterm infants indicate no negative effects of LCPUFA supplementation on growth [8, 9]. Further analyses using raw data from individual infants support these findings and show no growth deviations in infants supplemented with n-3 LCPUFA alone or in combination with AA [9].

Nevertheless, based on the composition of breast milk, most infant formula products contain a combination of DHA and AA, and this is indeed the most commonly studied combination for infants with regard to neurodevelopmental outcome. Our recent systematic review and meta-analysis examining the effects of LCPUFA-supplemented vs. control formulas on neurodevelopment of preterm infants identified seven trials with relevant outcomes, five of which assessed a combination of DHA and AA [10]. In the meta-analysis of all seven trials, infants fed LCPUFA-supplemented formula and tested with the Bayley Scales of Infant Development Version II (BSID-II) had a mental development index (MDI) that was 3 points higher than infants fed control formula (weighted mean difference, WMD, 3.44, 95% CI: 0.57–6.31, n = 879, p = 0.02; fig. 1a) [11–17]. This difference was also evident in the subgroup of five trials that examined trials that supplemented with a combination of n-3 LCPUFA and AA (WMD 3.44, 95% CI: 0.06–6.81, n = 721, p = 0.05; fig. 1b) [11, 12, 14, 15, 17]. Fewer MDI data were available for infants tested with BSID-I and the control and treatment groups did not differ (WMD –4.09, 95% CI: –9.85 to 1.67, n = 97, p = 0.16). Overall, no significant difference in MDI was observed between infants fed control or LCPUFA-supplemented formula when MDI data from both BSID-I and BSID-II assessments were combined (WMD 2.13, 95% CI: –0.88 to 5.15, n = 976, p = 0.16; fig. 1a). In our meta-analyses, the incongruence observed between the MDI scores and version of the BSID added to the heterogeneity between trials and contributed to the need to apply random effects models. It was not possible to combine the BSID-I and II data in a meaningful way because the differences between trials contributed to a greater diversity in responses than expected. The differences between trials may arise from the sample population studied, the way the intervention was applied, the types of outcomes or trial methodology. We have limited confidence in the BSID-I outcome as these data were generated from two trials with small sample sizes and methodological limitations [16, 17].

In an equivalent meta-analysis involving term infants, LCPUFA supplementation of infant formula resulted in no effect, positive or negative, on MDI scores compared with control regardless of the version of BSID used for neurodevelopmental assessment (WMD –0.26, 95% CI: –2.30 to 1.78, n = 960, p = 0.80; fig. 2a) [18–23]. In term infants, three small trials were available to conduct meta-analyses including the subgroup of studies that assessed n-3 LCPUFA alone vs. control, while six studies assessed n-3 LCPUFA+AA vs. control (fig. 2b, c). These analyses indicated no clear effect of the type of LCPUFA supplementation on MDI scores, suggesting that there is little dif-
A differential effect on infant development if DHA is used alone or in combination with AA. However, power was limited for the analysis including studies that supplemented with only n-3 LCPUs, and moderate heterogeneity was evident in the studies testing n-3 LCPUs+AA and using Bayley II. Larger sample populations are needed to strengthen the degree of confidence in the result.
<table>
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<tr>
<th>Study or Subgroup</th>
<th>LCPUFA Control</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
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<th>Weight</th>
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<td>Mean</td>
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<td>Total</td>
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<td>IV, Random, 95% CI</td>
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<tr>
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<td>Auestad 2001</td>
<td>96.7</td>
<td>10</td>
<td>117</td>
<td>97.8</td>
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<td>$-1.10 [-4.07, 1.87]$</td>
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<td>Birch 2000</td>
<td>104.2</td>
<td>11.8</td>
<td>36</td>
<td>98.3</td>
<td>8.7</td>
<td>20</td>
<td>11.2%</td>
<td>$5.90 [0.48, 11.32]$</td>
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<td>15.4</td>
<td>135</td>
<td>105.4</td>
<td>15</td>
<td>155</td>
<td>20.9%</td>
<td>$-2.70 [-6.21, 0.81]$</td>
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<td>Lucas 1999</td>
<td>94.2</td>
<td>12.8</td>
<td>125</td>
<td>94.7</td>
<td>13.4</td>
<td>125</td>
<td>22.9%</td>
<td>$-0.50 [-3.75, 2.75]$</td>
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<td>Subtotal (95% CI)</td>
<td>413</td>
<td>348</td>
<td>80.4%</td>
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<td>$-0.19 [-2.97, 2.59]$</td>
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<td><strong>Heterogeneity:</strong></td>
<td>Tau$^2$ = 4.50; Chi$^2$ = 7.01, df = 3 ($P = 0.07$); I$^2$ = 57%</td>
<td>Test for overall effect: Z = 0.14 ($P = 0.89$)</td>
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| **1.2 BSID Version I** | | | | | | | | | | |
| Makrides 2000 | 111.3 | 16 | 44 | 110 | 12 | 21 | 7.4% | $1.30 [-5.68, 8.28]$ | | |
| Scott 1998 | 104.5 | 15 | 89 | 105 | 14 | 45 | 12.2% | $-0.50 [-5.64, 4.64]$ | | |
| Subtotal (95% CI) | 133 | 66 | 19.6% | | | | | $0.13 [-4.01, 4.27]$ | | |
| **Heterogeneity:** | Tau$^2$ = 0.00; Chi$^2$ = 0.17, df = 1 ($P = 0.68$); I$^2$ = 0% | Test for overall effect: Z = 0.06 ($P = 0.95$) | | | |

| **Total (95% CI)** | 546 | 414 | 100.0% | | | | | $-0.26 [-2.30, 1.78]$ | | |
| **Heterogeneity:** | Tau$^2$ = 1.98; Chi$^2$ = 7.27, df = 5 ($P = 0.20$); I$^2$ = 31% | Test for overall effect: Z = 0.25 ($P = 0.80$) | | | |

**Fig. 2.** Meta-analysis of RCTs comparing neurodevelopment of term infants fed LCPUFA-supplemented formula compared with an unsupplemented control formula. Infants were assessed with the BSID MDI between 12 and 18 months of age. Subgroup analyses were based on the version of the BSID used for assessments. **a** All trials that tested LCPUFA-supplemented formula vs. control formula. **b** Trials that tested formulas supplemented with n-3 LCPUFA alone.
When to Supplement with LCPUFA

DHA accretion to neural tissues peaks during the fetal brain growth spurt in the last trimester of pregnancy. Infants born preterm are denied the full gestation period to accumulate DHA and consequently have lower brain concentrations of DHA than their full-term counterparts [24]. This may explain the fact that LCPUFA supplementation trials involving preterm infants more consistently report visual and developmental benefits, while the observations from studies involving term infants are less clear with regard to visual development and report little or no benefit in more global developmental outcomes.

As many pregnant women in Westernized countries have low dietary intakes of DHA, there is now increasing international interest in whether higher DHA intakes during pregnancy also benefit the cognitive outcomes of infants born at term. A number of cohort studies have investigated the relationship between maternal seafood intake, which is a rich source of DHA, during pregnancy and developmental outcomes of children. These studies involved between 389 and 8,946 women and all reported that fish or seafood intake in pregnancy was associated with benefits including better motor skills and social development of children at 18 months of age [25], higher receptive vocabulary at 3 years [26], higher intelligence quotient (IQ) at 4 years [27] and lower rates of intellectual impairment at 8 years [28]. Although these associations were corrected for multiple confounding factors, the possibility
exists that some factor other than DHA in seafood is driving these associations. Other cohort studies that related blood DHA concentrations during or at the end of pregnancy with later child development have added strength to the seafood intake studies. For example, higher DHA status has been reported to be associated with more organized sleep patterns in early infancy [29], improved attention and distractibility through to 2 years [30, 31], better motor development and fewer internalizing behavior problems at 7 years [32, 33] relative to children with a lower perinatal DHA status. Despite the consistency of these associations, it is not possible to infer a causal link between increased DHA exposure in pregnancy and improved cognitive outcomes in children from these data alone because it is not possible to exclude the presence of residual confounding. Therefore, evidence from RCTs is essential to establish the extent of benefit between gestational DHA supply and cognitive development in childhood.

Evidence from RCTs: Effect of Prenatal DHA Supplementation on Childhood Development

To date there have been four RCTs involving DHA supplementation during pregnancy that have measured cognitive development in childhood [34–37] (one trial has multiple publications [37–39]). All trials involved supplementation of women from mid-pregnancy to delivery or later with a DHA-rich fish oil. Three trials tested doses of DHA ranging from 1.2 to 2.2 g/day, whereas one supplied ~300 mg DHA/day in muesli bars [34]. Results from these trials were mixed; no difference in early cognitive development was observed in Fagan Infantest at 6 or 9 months [34, 37], global development at 10 months [35], language or behavior at 30 months [36], or IQ at 7 years [38] between the supplemented and control groups. In contrast, prenatal DHA-supplementation resulted in improved problem solving at 9 months [34], hand-eye coordination at 30 months [36] and IQ at 4 years [39]. All trials had small sample sizes (between 15 and 125 participants per group) and thus were underpowered for assessing subtle to moderate improvements in cognitive development. Furthermore, poor reporting of concealed allocation [34, 35] and high attrition rates between 26 and 74% [35, 36, 39], make random error or bias possible in all of the RCT findings. At least four well-designed trials are currently in progress assessing the effect of DHA supplementation (ranging from 400 to 900 mg/day) during pregnancy on developmental outcomes of the offspring, and should provide robust answers regarding DHA intake and early childhood development.

Dose of LCPUFA

The new phase of LCPUFA research is focusing on dose. Postmortem tissue analyses of stillbirths suggested that in utero whole body accumulation of
DHA was in the order of 60 mg/kg per day [40]. We tested whether increasing the amount of dietary DHA, from ~20 mg/kg per day to levels that we calculated to provide the fetal accumulation rate (~60 mg/kg per day), would improve neurodevelopment in infants born <33 weeks gestation [41]. DHA enrichment of breast milk fed to infants was achieved through maternal supplementation with tuna oil or direct addition to infant formula. In this large and inclusive trial, we showed that infants fed the DHA-enriched diet had better visual development in infancy [42]. We also demonstrated an improvement in mean MDI at 18 months’ corrected age that did not reach statistical significance (p = 0.2), although there were 50% (5.2 vs. 10.5%, p = 0.03) fewer children with significant cognitive delay in the high-DHA (60 mg/kg per day) group [41]. Furthermore, DHA-supplemented girls and infants born weighing <1,250 g had a 5-point improvement in mental development scores compared with control [41]. Even in these responsive groups, there was evidence of a dose response indicating that further gains could be made. Regression analysis indicated that every 1% increase in DHA in breast milk fats was associated with an increase in MDI score of around 4 points (95% CI: -0.65 to 8.93, p = 0.08) [41]. The efficacy of about 90 mg/kg per day of DHA in infants born <1,500 g was recently reported, showing improved problem solving and better recognition memory at 6 months’ corrected age [43], indicating that higher DHA doses than currently found in infant formulas or the breast milk of women with Westernized diets may be needed for infants born preterm.

**How Does DHA Work and Does This Relate to DHA Dose?**

New animal data show that high-dose DHA is neuroprotective. Huang et al. [44], using an animal model of thoracic spinal cord compression, have established that axonal injury was reduced and locomotor recovery improved when animals received DHA compared with the saline-treated control group. In contrast, animals treated with AA had a significantly worse outcome than controls, indicating specificity of effect to DHA [45]. Two conditions were necessary to achieve the best outcomes – a high DHA dose (8–10 times the treatment dose in our trial with preterm infants [41] and the absence of a delay between injury and DHA administration. Two mechanisms have been suggested from these animal studies – increase in neurite growth and down-regulation of inflammation. There has been an explosion of information concerning this latter point and the anti-inflammatory mediators that are derived from DHA (docosanoids) that have the capacity to dampen acute inflammatory responses and return homeostasis. A complex series of E and D resolvins along with neuroprotectin D1 are now known to work in concert to overcome neural damage from the inflammatory response when DHA was around 2% dietary fats. In this regard, there are a number of case studies in which high-dose DHA has been infused intravenously to patients with major brain
or spinal cord injury and resulted in dramatic recovery of function [46]. It is possible that high-dose DHA is not only an important building block for the preterm brain but may be neuroprotective in the critical first days and weeks following preterm delivery. These data have raised new questions about DHA dose as well as its timing.

We are beginning a new era in LCPUFA research in infancy. We have moved from a period where conservative amounts of DHA were tested, often in studies of limited power. We are now trying to evaluate the potential benefits of DHA supplementation that attempt to mimic the levels of DHA supplied in utero. However, even these levels are based on estimates from fetuses from women who consumed low n-3 LCPUFA diets and may have limited validity. Future intakes of DHA for preterm infants may prove to be different to current levels.

**References**


LCPUFA in Neurodevelopment and Growth


Discussion

Dr. Martorell: As you know, a group of us at Emory University and the National Institute of Public Health of Mexico are conducting a randomized controlled trial of DHA versus placebo in 1,000 pregnant women. We just got funded to continue the follow-up of the newborns from 2 to 5 years of age and our hope is to receive more funding to extend the follow-up even further. My question is why did you specify 7 years of age as the target age for follow-up? Secondly, what types of outcomes would you recommend be measured in children of school age?

Dr. Makrides: I made the comment about 7 years of age because the IQ that you can measure at 7 is more predictive of adult IQ than developmental quotient measured at 18 months or 2 years. I would be more confident about extrapolating an IQ at 7 to adult IQ than I would be about the developmental quotient at 18 months.

Dr. Martorell: And beyond IQ, what else would you measure?

Dr. Makrides: The other assessments we are undertaking at 7 years include executive function, various memory assessments as well as a number of behavioral and attention assessments.

Dr. Giovannini: Do you think that arachidonic acid and DHA have separate roles? The second question is, we have many studies about the absolute amount of DHA, but what is your opinion about suggesting DHA in the first 12 months of life including the complementary feeding period. And would there be a difference in the dose for males and females?

Dr. Makrides: The first question relates to arachidonic acid. There are no human studies that have been specifically designed to evaluate the specific individual effect of arachidonic acid. Arachidonic acid has always been added to infant formulas either
for balance or to avoid the reduction in blood AA that is associated with DHA supplementation. I have suggested to a number of companies that we should try and evaluate the specific role of arachidonic acid but that hasn’t been taken up. In the absence of any data, I don’t know the specific role of arachidonic acid. The brain accretion data suggest that arachidonic acid accretes very nicely without specific supplementation. There is also no clear effect on growth. Whether arachidonic acid has other effects beyond growth and development I don’t know.

In terms of whether LCPUFA supplements are required for term infants during the period of complementary feeding, the available data are not very convincing, so I personally don’t see any reason for supplementation for infants that are healthy and born at term.

Dr. Giovannini: What can you tell us about the safety problem of fish oil and single cell oil in infant formulas?

Dr. Makrides: I think all the fish oils used in infant formulas are very carefully processed. In fact the fractionation and processing process basically ensures that there are no pesticides or heavy metals, so the notion that fish oils added to infant formula also have environmental contaminants is actually not true. Further, both single cell oils and fish oils are in the triglyceride form. Chemically they are the same. The fish actually get the DHA from eating algae so it’s just further along the food chain.

Dr. Hüppi: If we look at the distribution of DHA in the developing brain, it seems to be highly concentrated in the somatosensory and motor cortices. Given that these are also active regions of myelination and that myelination has an effect on motor development, did your studies look at the impact on fine motor development in these preterm children, because they are often described as having what we call the minimal CP or clumsiness.

Dr. Makrides: The rate of CP in our DINO trial was around 5%, and it was the same in both groups [1]. We of course measured psychomotor development, and the groups did not differ. I am not sure how well the PDI measures fine motor skills at 18 months of age. We are certainly including some more detailed assessments at 7 years.

Dr. Cooke: With protein-energy deficiency, Δ-5 and Δ-6 desaturase activity decreases and the conversion of linolenic to eicosapentaenoic and docosahexanoic decreases [2]. Perhaps greater protein requirements in boys put them at a greater risk for protein-energy deficiency, therefore reduced EPA and DHA synthesis. Can you comment?

Dr. Makrides: We certainly have quite detailed intake data, and we have not yet looked at that according to sex differences. We also have blood spots that we are analyzing for the carnitines. I agree with you that it will important to tease out the requirements for boys and girls for fatty acids, protein and energy and how they interrelate.

Dr. Lucas: There are two sorts of people in science, lumpers and splitters, people who like to lump everything together and do meta-analysis and people who like to look at the detail, and it makes a huge difference to the LCPUFA field, which one you are, because if you put everything together you find nothing. We have done four large robust randomized trials of LCPUFA using completely different sources, and depending on the trial we have been able to make neurodevelopment better or have no effect or make it significantly worse (6-point reduction in IQ in one of our studies), and we have been able to make growth significantly better, significantly worse or have no effect. I am not necessarily suggesting that that’s related to the LCPUFA, it could be related to undesirable aspects of the source for instance, but do you think that there is a danger in meta-analysis that you could lose information?
Dr. Makrides: I certainly think that we need to consider both approaches, and that's actually the reason why I have considered the specific subgroups and whether they contribute to the heterogeneity. This approach is recommended to test the sensitivity of the meta-analysis, although meta-analysis of this sort does have some limitations when you are looking at outcomes like growth, where it's a dynamic process and measures are repeated over time, rather than an outcome that is categorical. That's why we went to the complex modeling. I take your point about the developmental effects, but it is actually quite difficult to discuss the potential negative effect you refer to. The data have not been published, and I have no appreciation of whether there are other issues in the study design that could have influenced those outcomes. For example, attrition rates could influence the integrity of the randomization. The whole field is bedeviled by the fact that formula-fed infants are particularly difficult to follow up long-term, and many of the studies have high attrition rates and the children you follow up are different from the ones that do not attend. Therefore, the quality of the individual studies also becomes important, and the quality of the meta-analysis is only as good as the individual studies. Having said this, the systematic review with an appropriate sensitivity analysis based on trial quality still gives us the best way of understanding the totality of evidence.

Dr. Lapillonne: I have a question which relates to preterm infants. Don't you think we are still missing a very critical period for DHA supplementation which is the period during which the preterm infants receive parenteral nutrition? Should we take this early DHA deficit into account in order to make some estimates for the DHA needs during enteral nutrition?

Dr. Makrides: I couldn't agree more. If we take the hypothesis that the babies born at the earliest gestation have the highest requirements, they are also the babies that take the longest to get to full enteral feeds and therefore receive the lowest DHA dose. They are the ones that will have the greatest deficit, so I agree with you that that's a gap in research. I think the other gap in research that hasn't been addressed is the requirement of the SGA baby. Most studies have focused on term babies with birthweights greater than 2.5 kg or preterm babies born before 34 weeks.

Dr. Manzoor Hussain: You said that you included all preterm babies with diseases, so did you find any differences between those with insults and those without?

Dr. Makrides: I don't have the data with me for all clinical outcomes, but there were no differences between the groups in the rate of sepsis, necrotizing enterocolitis, or intraventricular hemorrhage [1]. The higher DHA group did have fewer babies who required oxygen treatment at 36 weeks, so there was less chronic lung disease in the high DHA group as opposed to the control group [1].

Dr. Islam: What is your comment on the companies that are now aggressively marketing EPA and DHA as very important formula constituents? Do you think it's justified?

Dr. Makrides: I think that the data relating to term infants are not strong in supporting a great benefit. There are authors in the field that interpret the data in two ways. Some authors say that some studies do show visual acuity benefits and we should give LCPUFA to all babies because there might be a subgroup of babies that might respond. There are others that are more cautious. They worry about the long-term benefits that are not clearly shown and the need for an assessment of long-term risk.

Dr. Adair: We have focused on growth and development, but can you comment on the effects on the immune system?

Dr. Makrides: The data from high-quality randomized controlled trials are limited. There are a couple of small studies that suggest that LCPUFA supplementation may change some of the cellular populations and the balance of cytokines. What
that actually means in terms of being able to fight off an infection or being able to modulate one's propensity to allergy is not clear. The big interest is in terms of altering the immune system in such a way that it's less prone to allergies, and that's one of the reasons why in our pregnancy study we have allergy as one of the primary outcomes.

References