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Essential Fatty Acid Supplementation and Early Inflammation in Preterm Infants: Secondary Analysis of a Randomized Clinical Trial

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Keywords
Inflammation · Premature infant · Nutrition · LCPUFA

Abstract
Introduction: Postnatal inflammation is associated with increased mortality and adverse outcomes in preterm infants. The essential fatty acids arachidonic acid (ARA) and docosahexaenoic acid (DHA) are precursors of lipid mediators with a key role in resolving inflammation. Our aim was to investigate the effect of ARA and DHA supplementation on systemic inflammation in very preterm infants and to identify clinical factors associated with early inflammation. ***Methods:*** Secondary analysis of data from a randomized clinical trial (ImNuT study). Infants with gestational age (GA) less than 29 weeks were randomized to receive a daily enteral supplement with ARA 100 mg/kg and DHA 50 mg/kg (ARA:DHA group) or MCT oil (control group) from the second day of life to 36 weeks postmenstrual age. ARA, DHA, and four proinflammatory cytokines (IL-1β, IL-6, IL-8, and TNF-α) were analyzed in repeated dried blood samples from birth to day 28 and the area under the curve (AUC) for each variable was calculated. ***Results:*** The intention to treat population included 120 infants with mean (SD) GA 26.4 (1.7). The ARA:DHA group had significantly lower IL-6 levels from day 3 to day 28 compared to the control group, mean difference AUC $\log_{10}$ (95% CI): 0.16 (0.03–0.30) pg/mL, $p = 0.018$. There was no correlation between ARA or DHA blood concentrations and cytokine levels. Having a low gestational age was independently associated with increased levels of all cytokines during the first 4 weeks of life. ***Conclusions:*** Enhanced supplementation with ARA and DHA may modulate inflammation in very preterm infants.

Introduction

Fetal and postnatal inflammation is associated with increased mortality and adverse outcomes in extremely preterm infants [1]. A better understanding of the mechanisms behind inflammation is important for improved neonatal care. The specialized pro-resolving lipid mediators (SPMs) derived from the long-chain polyunsaturated fatty acids (LCPUFAs), arachidonic acid (ARA) and docosahexaenoic acid (DHA), play key roles in the

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resolution of the inflammatory cascade [2]. ARA is the precursor of prostanoids and leukotrienes that contribute to inflammation, but it is also the precursor of a group of potent resolving signal molecules called lipoxins [3]. DHA mainly influences the inflammatory process through the formation of pro-resolving resolvins, protectins, and maresins, in addition to inhibiting the production of proinflammatory cytokines [4].

Infants born extremely preterm are deprived of placental transfer of LCPUFAs occurring during the third trimester and low cord blood concentrations of ARA and DHA at birth have been associated with increased systemic inflammation [5, 6]. Postnatally, the nutritional provision of ARA and DHA is insufficient to meet the requirements of preterm infants, resulting in persistent LCPUFA deficiency through early life [7].

Low blood concentrations of ARA and DHA are associated with an increased risk of neonatal morbidities in preterm infants, including bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) [8, 9]. However, studies of LCPUFA supplementation to premature infants have shown divergent results. Postnatal enteral DHA supplementation to infants with gestational age (GA) < 29 weeks may increase the risk of bronchopulmonary dysplasia [10], but in a recent randomized trial of supplementation with ARA and DHA in a 2:1 ratio, we showed improved short-term respiratory outcomes in a similar study population [11]. A balanced intake of ARA and DHA in extremely preterm infants also reduced the incidence of severe ROP in a randomized controlled trial by Hellstrom et al. [12]. One possible explanation for the clinically beneficial effects of ARA and DHA supplementation is their pro-resolving inflammation properties. Few studies have investigated the correlation between postnatal inflammation and the LCPUFA status in preterm infants. The aim of this study was to evaluate the effect of enhanced ARA and DHA supplementation on systemic inflammation during the first 4 weeks of life in preterm infants with GA <29 weeks, and to identify clinical factors associated with early systemic inflammation.

Materials and Methods

Study Design and Participants

A secondary analysis of a double-blind randomized controlled trial, the Immature, Nutrition Therapy (ImNuT) study, registered at Clinicaltrials.gov ID: NCT03555019. ImNuT was a single-center study conducted at Oslo University Hospital. A detailed description of the study design was published in 2020 [13]. The primary outcome of ImNuT was to determine the effect of ARA and DHA supplementation on brain growth and maturation in very preterm infants. Secondary outcomes included quality of growth, incidence of inflammation and neonatal morbidities, cardiovascular health, and neurodevelopment.

Infants born at Oslo University Hospital with GA <29 weeks were eligible to participate in the study. Exclusion criteria were congenital malformations, chromosomal abnormalities, or critical illness with short life expectancy. Participation required written informed parental consent within 48 h after birth.

Randomization and Blinding

We used a computer-generated list of random numbers for the allocation of participants to the two treatment groups. The block size was randomly alternated between 4, 6, and 8. Randomization was stratified according to growth status at birth: small for GA or not, with an allocation ratio of 1:1 within each block. In multiple births, siblings were assigned to the same treatment group. All caregivers and investigators, except the study pharmacist, were blinded to group allocation.

Trial Intervention

The intervention group received an enteral supplement (Formulaid™, DSM Nutritional Products Inc.) consisting of ARA 100 mg/kg and DHA 50 mg/kg, while the control group received medium-chain triglycerides (MCT-oil™, Nutricia). Fatty acid supplementation was administered as a daily bolus in the feeding tube from the second day of life until 36 weeks postmenstrual age. All study participants followed a standardized nutritional protocol that accommodated international recommendations (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000530129).

Outcomes

We obtained whole blood samples (10 μL) at days 1 (baseline), 3, 5, 7, 14, and 28 for the evaluation of four proinflammatory cytokines: IL-1β, IL-6, IL-8, and TNF-α. To determine postnatal blood levels of ARA and DHA, we obtained whole blood samples (10 μL) at inclusion and then on days 3, 7, 14, 21, and 28. The samples were collected on Mitra® sticks, dried in room air, and stored at −80°C until analyzation. The method for preparation and cytokine analysis is described in online supplementary material. The method used for the analysis of ARA and DHA has previously been reported [11].

Statistical Analysis

The sample size calculation was based on the primary outcome of the ImNuT trial; 120 infants would provide 80% power to detect a 0.04 difference in mean diffusivity (mm^2/s) in the white matter tracts on magnetic resonance imaging at term equivalent age [13]. Comparisons of cytokine blood levels between groups were performed in the intention-to-treat (ITT) population. The blood levels of the respective cytokines were used to calculate the area under the curve (AUC) as a measure of the total cytokine burden from days 3 to 28. Cytokine values were logarithmically transformed before analysis due to an asymmetrical distribution. For comparison of cytokine blood levels between groups, we used an independent *t* test.

The observational analysis was performed on the ImNuT cohort, but patients who died or were withdrawn before 28 days were not included in the analysis due to missing clinical outcome data. To study the correlation between the AUC (days 1–28) of ARA,

Table 1. Baseline and clinical characteristics up to day 28 of the ITT population and the study population included in the observational analysis

	ITT population		Observational study population
	control (n = 60)	ARA:DHA (n = 60)	control + ARA:DHA (n = 110)
Baseline characteristics			
Mothers			
Antenatal glucocorticoids, any dose	60 (100)	60 (100)	110 (100)
Cesarean delivery	38 (63.3)	29 (48.3)	59 (53.6)
Premature rupture of membranes	18 (30.0)	16 (26.7)	31 (28.2)
Preeclampsia	10 (16.7)	14 (23.3)	22 (20.0)
Clinical suspicion of maternal infection[1]	10 (16.7)	12 (20.0)	19 (17.2)
Infants			
Gestational age, weeks	26.2 (1.6)	26.6 (1.7)	26.5 (1.6)
Birth weight, g	833 (255)	879 (241)	871 (248)
Small for GA	12 (20.0)	11 (18.3)	20 (18.2)
Male sex	31 (51.7)	35 (58.3)	61 (55.5)
Multiple birth	13 (21.7)	16 (26.7)	28 (25.5)
Apgar score at 5 min	7 (6-8)	8 (7-9)	8 (6-8)
Early-onset septicemia[2]	3 (5.0)	10 (16.7)	12 (10.9)
IL-6 day 1, pg/mL	10.0 (5.9–18.3)	8.2 (4.8–19.0)	8.5 (5.0–18.2)
Clinical characteristics			
Intraventricular hemorrhage grade III-IV	4 (6.7)	7 (11.7)	9 (8.2)
Necrotizing enterocolitis	2 (3.3)	2 (3.3)	3 (2.7)
Mechanical ventilation >7 days	30 (50.0)	22 (36.7)	50 (45.5)
Postnatal steroids	28 (46.7)	21 (35.0)	48 (43.6)
Patent ductus arteriosus requiring treatment	27 (45.0)	23 (38.3)	48 (43.6)
One or more episodes of septicemia[3]	26 (43.3)	28 (46.7)	50 (45.5)

Data are presented as n (%), mean (SD), or median (IQR). ARA, arachidonic acid; DHA, docosahexenoic acid; IQR, interquartile range; SD, standard deviation. [1]Maternal fever in association with leukocytosis or elevated CRP. [2]Positive blood culture or clinical signs of infection with CRP >10 pg/mL within 72 h after birth. [3]Including early- and late-onset septicemia.

DHA, and cytokine blood levels, we used Spearman's rank test. A backward stepwise linear regression model was performed to explore clinical factors associated with blood levels of IL-1β, IL-6, IL-8, and TNF-α. In addition to randomization group, we included the following variables known to be associated with inflammation: GA, small for GA status (SGA), sex, mechanical ventilation >7 days, and one or more episodes of septicemia. A p-value threshold of 0.2 was set as the elimination criteria for the variables included in the final model. The reported unstandardized coefficients (B) reflect changes in the logarithmic transformed cytokine AUCs. For the calculation of the AUC, median levels for cytokines and mean levels for fatty acids at each time point, based on treatment group inherence, replaced missing values in the data set. For all analyses, we considered a p value of <0.05 statistically significant. IBM SPSS Statistics version 28.0 was used in the statistical analyses.

Results

Study Participants

From April 2018 to January 2021, 121 infants with GA <29 weeks were randomized. 61 infants were assigned to the control group and 60 to the ARA:DHA group. One patient assigned to the control group was excluded from the trial due to a chromosomal abnormality diagnosed after randomization. The ITT population included 120 infants, out of whom 110 infants had complete clinical outcome data at 28 days of age and were included in the observational analysis (shown in Fig. 1). The baseline and clinical characteristics of the ITT population and the observational study population are presented in Table 1. A detailed description of the observational study population and excluded patients is found in online supplementary Table 2.

Comparison of Cytokine Levels between Treatment Groups

A total of 584 blood samples were obtained for cytokine analyses, out of which 45 random samples were destroyed due to machine error during the analyzation process. The number of blood samples included in the final analysis was distributed similarly between the treatment groups (online

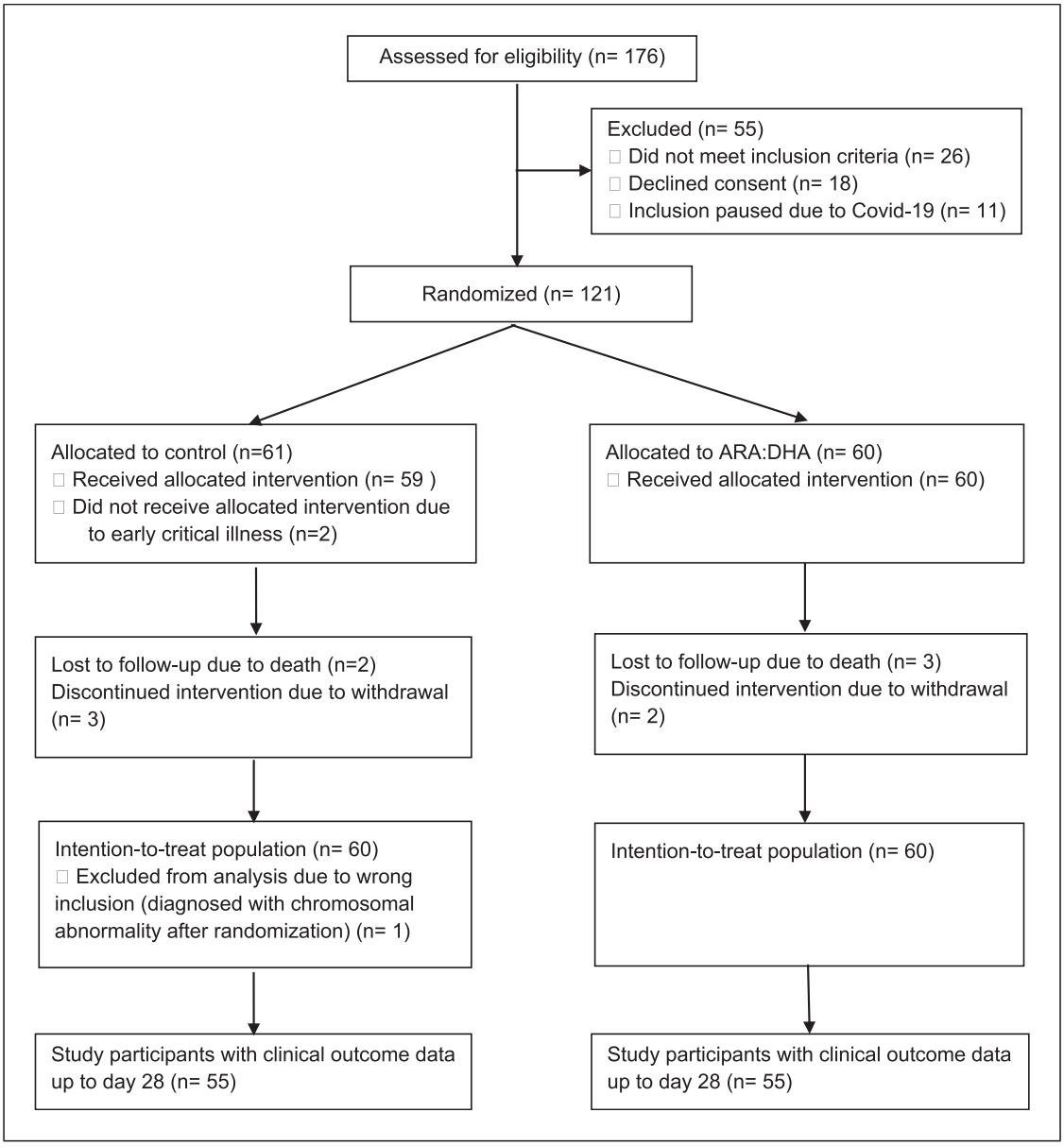

Fig. 1. Flow diagram of enrollment, randomization, and follow-up of study participants included in the ImNuT trial.

suppl. Table 3). IL-6 blood levels were significantly lower in the ARA:DHA group compared to the control group (MD pg/mL [95% CI]) on day 5 (0.20 [0.01–0.39], p = 0.04) and at day 14 (0.27 [0.02–0.52], p = 0.04). Furthermore, the total IL-6 burden assessed as AUC days 3–28 was significantly lower in the ARA:DHA group compared to the control group (MD pg/mL [95% CI] 0.16 [0.03–0.30], p = 0.018). At days 3 and 5, the levels of TNF-α were significantly lower in the ARA:DHA group, and at day 14, the concentrations of IL-1β were significantly lower in the ARA:DHA group compared to the control group. There were no statistically significant differences in the total cytokine burden of IL-8, IL-1β, or TNF-α between the study groups (Fig. 2a–d).

Correlations between LCPUFA Blood Concentrations and Total Cytokine Burden

We obtained 583 blood samples for analysis of ARA and DHA in relation to inflammatory markers. There were no statistically significant correlations between ARA

blood concentrations and IL-6, IL-8, IL-1β, or TNF-α blood levels from birth to 28 days of life. Neither was there a correlation between DHA blood concentrations and the four interleukins (Table 2).

Clinical Factors Associated with Inflammation

Having a low GA was associated with increased inflammation in the first 4 weeks of life, reflected in a significant increase in the AUC of all the four cytokines. Mechanical ventilation for more than 7 days was independently associated with an increase in blood levels of IL-8 (B 0.13, $p = 0.024$). Male infants and infants who had had one or more episodes of septicemia exhibited increased blood levels of IL-6 (male sex B 0.17, $p = 0.005$ and septicemia B 0.19, $p = 0.001$). The results are shown in Table 3.

Table 2. Correlations between total ARA and DHA blood concentrations (AUC mol%) and total cytokine blood levels (AUC pg/mL) from birth to day 28, $n = 110$

	ARA		DHA	
	Spearman's *r*	*p* value	Spearman's *r*	*p* value
IL-6	−0.16	0.09	0.08	0.39
IL-8	−0.13	0.17	−0.03	0.73
IL-1β	−0.14	0.14	−0.09	0.34
TNF-α	0.02	0.86	0.08	0.43

ARA, arachidonic acid; DHA, docosahexaenoic acid; AUC, area under the curve.

Discussion

In this secondary analysis of data from a randomized clinical trial, we found that daily supplementation with ARA 100 mg/kg and DHA 50 mg/kg in preterm infants led to significantly reduced levels of IL-6 from day 3 to day 28, compared to control treatment. Increased blood levels of IL-6 are considered to be a hallmark of fetal inflammation, a diagnostic marker of early-onset septicemia, and a risk factor for white matter injury [14]. In vitro studies have suggested that DHA administration reduces IL-6 expression in lipopolysaccharide-activated macrophages [15]. Similarly, in rats exposed to inflammation-induced brain injury, arachidonic acid injections led to reduced levels of IL-6 compared to saline injections [16]. To our knowledge, few clinical studies have evaluated the effect of ARA and DHA supplementation on inflammation in preterm infants. Skouroliakou et al. [17] demonstrated that administration of DHA-enriched intravenous lipid emulsion to preterm infants resulted in significantly lower IL-6 levels at the end of the intervention, compared to a lipid emulsion containing soybean oil. A recent pilot study randomized 21 infants with GA <32 weeks to receive enteral ARA and DHA supplementation in a 2:1 ratio or MCT oil and found that the intervention group had improved antioxidant-oxidant balance at 36 weeks postmenstrual age compared to the control group [18]. Taken together, these studies suggest that LCPUFA supplementation has the potential to reduce inflammation in preterm infants. In a recent publication from the ImNuT trial, we showed that the ARA:DHA group had a shorter duration of respiratory support and a lower mean oxygen demand during hospitalization, compared to the control group [11]. Since systemic inflammation is associated with respiratory morbidity, we speculate that the potential benefits of ARA and DHA supplementation on respiratory outcomes might be explained by the reduced IL-6 levels in the intervention group during the first 4 weeks of life.

An observational study by Hellstrom et al. [5] found that higher blood DHA concentrations the first postnatal day were correlated with lower levels of IL-6 in extremely preterm infants. In our study, we did not find a correlation between blood concentrations of ARA or DHA and cytokine levels, but this does not exclude an anti-inflammatory effect of LCPUFA supplementation. A more accurate method of evaluating the effect of LCPUFA supplementation on inflammation could be to measure the blood levels of SPMs derived from ARA and DHA. A study in term infants, randomized to receive a daily supplement of DHA and eicosapentaenoic acid (intervention) or olive oil (control) after birth up to 6 months of age, demonstrated that the intervention group had higher plasma levels of SPMs than the control group [19]. Studies in adults have shown a similar increase in SPMs after enteral supplementation with fish oil [20].

Systemic inflammation in preterm infants occurs mainly in the first 4 weeks of life, a time period often referred to as the "window of opportunity" to prevent future morbidity [21]. We found an independent association between low GA and an increase in all four cytokines in the first 28 days. Several endogenous and exogenous factors may explain this association. The immature immune system of infants with low GA leads to overexpression of proinflammatory cytokines, which in turn is insufficiently regulated by immunosuppressing T cells [22]. Infants with low GA are more frequently exposed to exogenous triggers of inflammation, such as

Table 3. Multivariable regression analysis of clinical factors associated with inflammation days 1–28 (cytokine $\log_{10}$ AUC pg/mL) presented with unstandardized coefficients (B), n = 110

	IL-6		IL-8		IL-1β		TNF-α	
	B	*p* value	*B*	*p* value	*B*	*p* value	*B*	*p* value
Randomization group (ARA:DHA group = 1)	−0.09	0.152		NI		NI		NI
GA (mean, weeks)	−0.12	<0.001	−0.06	0.020	−0.06	<0.001	−0.04	<0.001
MV >7 days		NI	0.13	0.024		NI		NI
Septicemia	0.19	0.001		NI		NI	0.06	0.064
Male sex	0.17	0.005		NI		NI		NI
Adjusted R^2	0.38		0.34		0.17		0.15	

B, unstandardized slope coefficient; GA, gestational age; MV, mechanical ventilation; NI, not included in the final model due to *p* value >0.2 during stepwise regression.

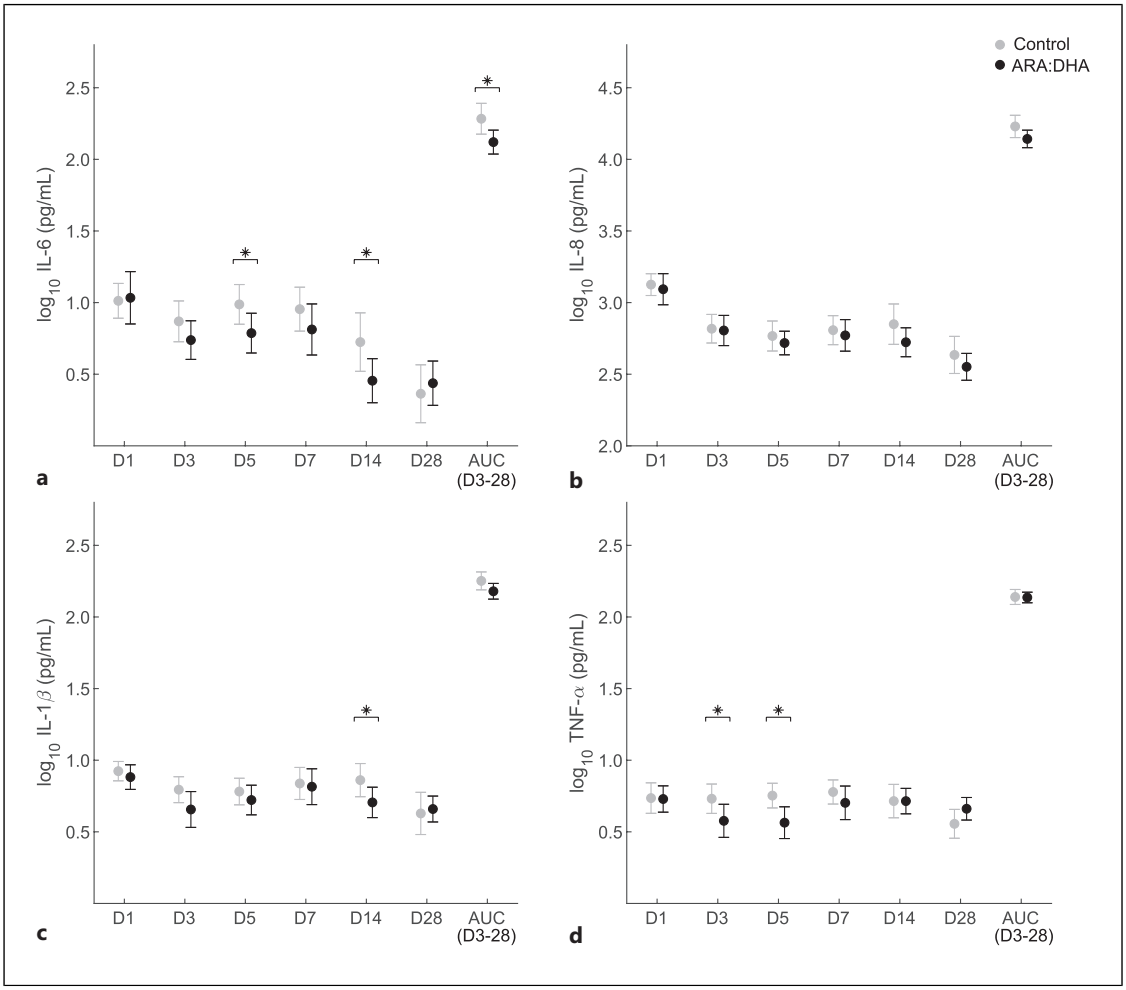

Fig. 2. Blood levels of IL-6 (**a**), IL-8 (**b**), IL-1β (**c**), and TNF-α (**d**) during the first 4 weeks of life, as well as AUC from day 3 to day 28 in the ARA:DHA group (black bars) and the control group (grey bars). Error bars show mean values with 95% CI, presented on a $\log_{10}$ scale. *$p < 0.05$.

painful procedures, prolonged mechanical ventilation, and oxidative stress. Previous studies have shown an association between mechanical ventilation in neonates and systemic inflammation, demonstrated by elevated blood levels of IL-8, TNF-α, and IL-1β [23]. We observed a similar association between mechanical ventilation for more than 7 days and increased levels of IL-8, even after adjustments for GA. Interestingly, we also found that male sex was associated with increased levels of IL-6. Gender differences in outcomes of extremely preterm infants have been reported in several studies. Male sex is associated with lower survival rates and increased burden of morbidities compared to females [24]. The mechanisms behind these gender differences are not fully understood, but sex-specific characteristics of the innate immune system appear to be of importance; male cord blood cells produced significantly higher levels of IL-6 in response to lipopolysaccharide stimulation compared to female blood cells [25]. Almost half of the participants in our study had one or more episodes of septicemia in the first 4 weeks of life, and we found that this correlated to higher total levels of IL-6. IL-6 is produced by neutrophils in the primary immune response to bacterial infections, and an elevation of IL-6 in serum has been regarded as an early biomarker of neonatal sepsis [26]. Septicemia triggers an acute flare-up of inflammation, but we did not take blood samples in relation to the actual event. However, there is evidence that these flare-ups may not be completely resolved. Preterm infants with elevated cytokines on day 7 were more likely to have elevated cytokines in weekly blood samples analyzed during the first month of life [21].

This study has several strengths and limitations. The double-blind randomized controlled study design ensured that both investigators and parents were unaware of treatment allocation, implying that the measured effect size was less prone to bias. The main limitation was the small sample size; the study was not powered to investigate differences in cytokine blood levels between treatment groups. Another weakness was that we did not have baseline data on maternal incidence of histologically diagnosed chorioamnionitis, which is a known risk factor for fetal and early postnatal inflammation.

In conclusion, the results of this study support the hypothesis that enteral supplementation with ARA and DHA may modulate inflammation in very preterm infants during the first 4 weeks of life. However, the relationship between LCPUFA status and systemic inflammation needs to be further investigated.

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Statement of Ethics

The study protocol of the ImNuT study was reviewed and approved by the Norwegian Regional Ethics Committee (2016-003700-31). All parents of study participants have given their informed written consent for study participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

K.W. included study participants, collected data, performed analysis, drafted the initial manuscript, and revised the manuscript. G.G. and M.F.A. included study participants, collected data, and reviewed the manuscript. Å.S.W. contributed with data analysis and reviewed the manuscript. A.H.P. assisted with statistical analyses and critically reviewed the manuscript. D.F. and T.S. supervised the study and provided critical feedback on the manuscript. S.J.M. designed and conceptualized the ImNuT study, supervised data collection, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be responsible for all aspects of the work.

Data Availability Statement

Data supporting the findings of this study are not publicly available due to content that could compromise the privacy of the research participants, but are available from the corresponding author (K.W.) on reasonable request.

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