National Recommendation

Enteral supplementation with docosahexaenoic acid (DHA) and arachidonic acid (ARA) in extremely preterm infants

Prepared by the Nutrition Working Group of the Swedish Neonatal Society.

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On behalf of the Swedish Paediatric Society and the Swedish Neonatal Society

Version 1.0 - 19 May 2026

NB: this is a ChatGPT translation of the original document in Swedish, found here:
https://neo.barnlakarforeningen.se/wp-content/uploads/sites/14/2026/08/Nationella-rekommendationer-DHA_ARA-final_V.2.pdf

Infants born before 28 weeks of gestation have high requirements for the long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid (ARA), and often develop low plasma concentrations of these fatty acids after birth. Enteral supplementation is necessary to ensure the recommended intake. Studies show that enteral supplementation with DHA and ARA reduces the risk of severe retinopathy of prematurity (ROP).

Recommendation

Infants born before 28 weeks of gestation are recommended to receive additional DHA and ARA supplementation from the first day of life, provided that the infant is receiving enteral intake (≥1 mL).

- Dosage: DHA 50 mg/kg/day and ARA 100 mg/kg/day, corresponding to 0.4 mL/kg/day of NeoMega36 (Neobiomics), a triglyceride oil based on Formulaid; see the dosing schedule below.
- The supplement is given once daily with a feed. Give a small amount of human milk, then the supplement, followed by the remainder of the feed.
- Do not give the supplement while the infant is fasting.
- DHA and ARA are given until hospital discharge, or at the latest until a postmenstrual age of 40 weeks.
- Supplementation is given regardless of whether the infant receives mother's own milk, donor human milk or infant formula, because standard nutrition is not considered sufficient to meet the DHA and ARA requirements of this patient group.
- A prerequisite for use of a DHA/ARA product in preterm infants is that the manufacturer can demonstrate sufficiently high product quality (see below).
- DHA/ARA supplementation should be reported to SNQ.

Dosing schedule

The dose is increased in 0.1 mL increments according to the dosing schedule. The maximum dose is 1 mL/day. The dose is calculated from birth weight until the current weight exceeds birth weight, and thereafter from current weight.

NeoMega36® (mL)	Weight
0.2	500 g
0.3	750 g
0.4	1000 g
0.5	1250 g
0.6	1500 g
0.7	1750 g
0.8	2000 g
0.9	2250 g
1.0	2500 g

Introduction

Extremely preterm infants have very high and specific postnatal nutritional requirements. Adequate nutrition is essential to support somatic growth, organ development and neurocognitive maturation. Infants born extremely preterm miss a substantial part of the nutrient transfer that normally occurs via the placenta during the third trimester of pregnancy. This includes the long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA) and arachidonic acid (ARA).

After extremely preterm birth, many infants develop low postnatal levels of both DHA and ARA. This is because provision through parenteral lipid emulsions, human milk and human milk fortification generally does not match intrauterine supply or compensate for the infant's requirements. The aim of this recommendation is to summarize the scientific evidence and describe a practical approach to enteral supplementation with DHA and ARA in extremely preterm infants.

Background: DHA and ARA

Docosahexaenoic acid (DHA, 22:6 n-3) and arachidonic acid (ARA, 20:4 n-6) are long-chain polyunsaturated fatty acids (LCPUFAs). They are present in all tissues but are particularly enriched in the brain and retina, where at term they constitute a substantial proportion of total fatty acids. DHA and ARA are important components of cell membranes, and their metabolites are important for neurobiological, visual and immunological processes (1-3).

During fetal life, DHA and ARA are transferred across the placenta. Maternal intake has a major influence on transfer of DHA to the fetus, whereas transfer of ARA appears to depend less on maternal intake. During the third trimester, DHA and ARA are also deposited in fetal adipose tissue, creating stores that can be used after birth (4).

During pregnancy, the fetus maintains higher relative blood levels of ARA than the mother, a phenomenon commonly referred to as biomagnification. This suggests that ARA has particular importance for early organ development. For DHA, a progressive increase relative to maternal levels is seen especially after 30 weeks of gestation, i.e. during the period when brain growth is particularly rapid. This enrichment continues postnatally during the first years of life (3, 5). Based on analyses of fetal tissue, intrauterine accretion during the third trimester has been estimated at approximately 43 mg/kg/day for DHA and 212 mg/kg/day for ARA (6).

Preterm infants have some endogenous capacity to synthesize DHA from alpha-linolenic acid (ALA, 18:3 n-3) and ARA from linoleic acid (LA, 18:2 n-6). Available data indicate, however, that this synthesis is insufficient to meet the needs of the preterm infant, particularly for DHA. Directly supplied DHA appears to be more effective than ALA in supporting DHA accretion in the brain. Endogenous synthesis also appears to be more efficient for ARA than for DHA (7).

After extremely preterm birth, the relative levels of both DHA and ARA fall rapidly compared with fetal levels, already during the first week of life (8, 9). Thereafter, DHA usually recovers progressively, whereas ARA often remains at lower levels until term-equivalent age (Figure 1) (8, 10). The relative decline is also influenced by the postnatal increase in the proportion of other fatty acids, particularly linoleic acid. A corresponding postnatal decrease is also seen in term infants (11), but under different physiological conditions than in extremely preterm infants.

Low postnatal levels of DHA and ARA have been associated with adverse outcomes in preterm infants. In particular, low levels of both DHA and ARA have been linked to an increased risk of retinopathy of prematurity (ROP) (12, 13). Higher DHA levels appear to be associated with a lower risk of severe ROP particularly when ARA levels are simultaneously adequate (14), suggesting that the balance between these fatty acids is important.

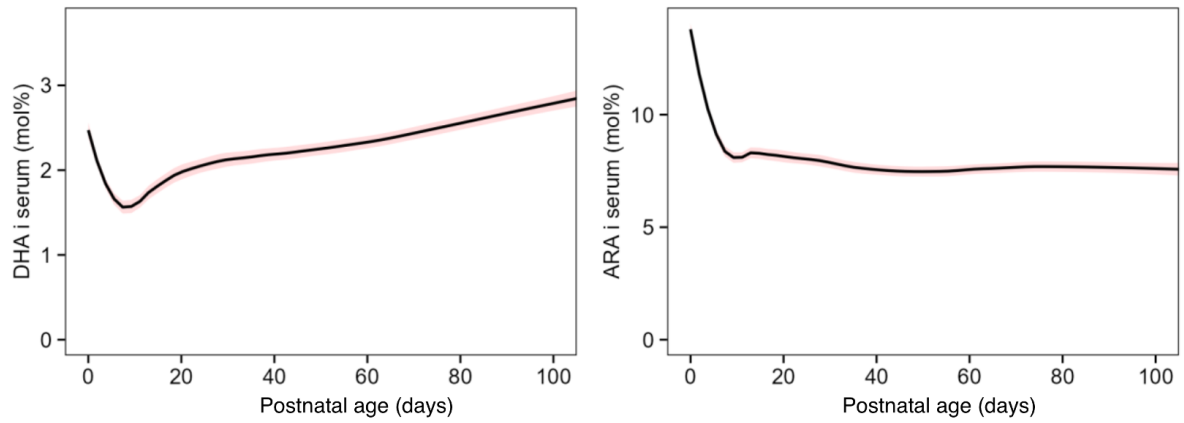

Figure 1. *Development of serum DHA (mol%) and serum ARA (mol%) during the first 100 postnatal days in extremely preterm infants in the Swedish Mega Donna Mega study (N = 204). The lines show the overall temporal development based on LOESS smoothing, and the shaded areas indicate 95% confidence intervals.*

Provision through human milk, fortification and parenteral nutrition

Human milk contains both DHA and ARA, usually with a higher proportion of ARA than DHA (15, 16). The content varies between individuals and is influenced mainly by the mother's diet, particularly with regard to DHA (1, 15). DHA and ARA concentrations in the mother's milk decrease over time, with proportions in colostrum and transitional milk that may be nearly twice those in mature milk (16, 17). Donor human milk generally contains lower levels of DHA and ARA than mother's own milk because it is usually collected later in lactation. Pasteurization of donor milk does not appear to substantially affect DHA and ARA concentrations (18), but it reduces lipase activity and may thereby impair fat absorption (19). Although these fatty acids are efficiently absorbed from human milk, the amounts are generally insufficient to compensate for the deficit that arises after extremely preterm birth.

Parenteral lipid emulsions make different contributions to DHA and ARA. Fish-oil-based emulsions (e.g. Omegaven, SMOFlipid) provide more DHA but little ARA, whereas plant-oil-based emulsions (e.g. Clinoleic, Intralipid) contain very small amounts of both (21). In infants, fish-oil-based emulsions result in higher blood DHA but lower ARA (22), whereas plant-oil-based emulsions result in low levels of both (9).

Some fortification products now also contain DHA and ARA, but in relatively low amounts. Taken together, this means that extremely preterm infants do not receive sufficient postnatal ARA and DHA without targeted supplementation. At present, there are no established parenteral lipid emulsions for infants containing both DHA and ARA.

ESPGHAN recommends an enteral intake for preterm infants of 30-65 mg/kg/day of DHA and 30-100 mg/kg/day of ARA (20). ESPGHAN does not provide recommendations for parenteral intake of these fatty acids. Calculations based on standard nutrition under Swedish conditions, without specific ARA and DHA supplementation, indicate that intake at full enteral feeding reaches at most just under half of ESPGHAN's recommended enteral intake. During periods of predominantly parenteral nutrition, provision is even lower, corresponding to only approximately 4-8% of the recommended enteral intake. The Swedish Neonatal Society therefore now recommends ARA/DHA supplementation for extremely preterm infants.

Outcomes in completed DHA:ARA studies

The scientific evidence for enteral supplementation with DHA and ARA in extremely preterm infants consists of a number of randomized studies with varying gestational ages, dosages, treatment durations and

outcome measures. In most studies, DHA and ARA have been given in a 1:2 ratio, which has been proposed to mimic intrauterine supply (21).

Overall, the studies indicate that combined supplementation favorably affects the fatty-acid profile and has positive effects on clinically relevant outcomes such as severe ROP.

The first randomized study included 141 infants with birth weight <1500 g and investigated supplementation of human milk with DHA and ARA from one week of age until discharge. The study reported improved cognitive outcomes at 6 months of age, but at long-term follow-up at 8 years no clear persisting difference between the groups was seen (22, 23).

In the Swedish multicenter Mega Donna Mega study, extremely preterm infants were randomized to DHA and ARA or control from <3 days of age until 40 weeks PMA. Treatment halved the risk of severe ROP and increased serum levels of DHA and ARA (10), without a clear difference in other neonatal morbidity. Secondary analyses showed no increased risk of BPD (24), larger brain volumes, particularly white matter (25), and better visual outcomes at 2.5 years of age, with some limitations in interpretation (26, 27).

In the Norwegian ImNuT study, 120 infants born at <29 weeks were randomized to DHA and ARA or placebo from day 2 until 36 weeks PMA (28). The intervention group showed more favorable white-matter microstructure, but no significant differences in other MRI measures. ROP was less frequent but not significantly so. Secondary analyses showed less need for respiratory support and oxygen, without a clear difference in BPD (29), as well as possible beneficial effects on growth, body composition and inflammatory markers (30, 31). At 2 years of age, no differences in neurocognitive development were observed (32).

Overall, completed studies show that enteral supplementation with ARA and DHA is feasible and appears safe at the doses studied. The strongest clinical evidence concerns a reduced risk of severe ROP and improved maturation of cerebral white matter.

Inflammation and safety

No studies to date have shown that supplementation with ARA in combination with DHA leads to increased levels of inflammatory markers in preterm infants. In some analyses, ARA and DHA levels have been associated with lower levels of inflammatory markers early postnatally (33, 34), suggesting that these fatty acids may have non-antagonistic and possibly synergistic effects.

Regulation and product quality control

It is important that product stability, shelf life, miscibility and quality are maintained when production is scaled up to larger quantities. From a regulatory perspective, it would be desirable for companies to apply for authorization to market these products as medicinal products. Until such medicinal products are available, it is the manufacturer's responsibility to demonstrate that the product is of sufficiently high quality.

Summary and proposed Swedish implementation

Available studies of combined enteral DHA and ARA supplementation in preterm infants have not demonstrated adverse effects. The strongest clinical evidence concerns a reduced risk of severe ROP. In addition, available data suggest beneficial effects on brain development, particularly white matter, visual function and postnatal inflammatory activity.

To facilitate follow-up of these new guidelines, it is important to register DHA/ARA supplementation in SNQ.

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Declaration of interests

Ann Hellström and Anders K Nilsson have, through the Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, received lecture and consultancy fees from Baxter and have given lectures for Neobiomics, but without remuneration. Magnus Domellöf has provided advice (participated in an advisory board) to Neobiomics, but without remuneration.