REPORT OF WORKSHOP

# Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development

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Koletzko B, Agostoni C, Carlson SE, Clandinin T, Hornstra G, Neuringer M, Uauy R, Yamashiro Y, Willatts P. Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development. Acta Pædiatr 2001; 90: 460–464. Stockholm. ISSN 0803-5253

This paper reports on the conclusions of a workshop on the role of long chain polyunsaturated fatty acids (LC-PUFA) in maternal and child health. The attending investigators involved in the majority of randomized trials examining LC-PUFA status and functional outcomes summarize the current knowledge in the field and make recommendations for dietary practice. Only studies published in full or in abstract form were used as our working knowledge base.

*Conclusions*: For healthy infants we recommend and strongly support breastfeeding as the preferred method of feeding, which supplies preformed LC-PUFA. Infant formulas for term infants should contain at least 0.2% of total fatty acids as docosahexaenoic acid (DHA) and 0.35% as arachidonic acid (AA). Since preterm infants are born with much less total body DHA and AA, we suggest that preterm infant formulas should include at least 0.35% DHA and 0.4% AA. Higher levels might confer additional benefits and should be further investigated because optimal dietary intakes for term and preterm infants remain to be defined. For pregnant and lactating women we consider it premature to recommend specific LC-PUFA intakes. However, it seems prudent for pregnant and lactating women to include some food sources of DHA in their diet in view of their assumed increase in LC-PUFA demand and the relationship between maternal and foetal DHA status.

**Key words:** *Arachidonic acid, dietary requirements, docosahexaenoic acid, essential fatty acids, infant nutrition*

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As investigators in the field of long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development, we have been involved in the majority of the randomized trials examining LC-PUFA status and function in pregnant and lactating women and in preterm and term infants. For this reason, the charitable and independent Child Health Foundation charged us to review the available scientific information on LC-PUFA during pregnancy, lactation and early life, and to give our conclusions on the role of LC-PUFA in maternal and child health. We met in a closed workshop without a public audience at Munich in Germany. At the conclusion of the workshop, all the scientific participants present reached a consensus on several aspects of the role of LC-PUFA. These consensus statements are summarized here under each topic discussed at the workshop, and are statements of the current knowledge in the field and recommendations for dietary practice. Only studies published in full or abstract form were used as our working knowledge base. We expect our consensus statements to require revision within the next few years as more data become available. We would

like to emphasize the need for additional research on all of these topics, particularly with regard to long-term effects on a broader range of functional outcomes.

## LC-PUFA metabolism

LC-PUFAs are synthesized from the nutritionally essential fatty acids, linoleic acid of the omega-6 (n-6) series and α-linolenic acid of the omega 3 (n-3) series (1). The predominant LC-PUFAs in human milk and tissues are arachidonic acid (AA, n-6) and docosahexaenoic acid (DHA, n-3) (2). Endogenous LC-PUFA synthesis from dietary precursors occurs from the first days of extra-uterine life, but considerable inter-individual variation in the rates of synthesis are observed in term and preterm infants (3, 4). The supply of linoleic acid and α-linolenic acid modulates AA and DHA synthesis (5, 6). However, the contribution of endogenous synthesis from α-linolenic acid to blood and tissue pools of infants does not match that of diets with preformed DHA (8–12). Similarly, neither linoleic acid nor the intermediate n-6 fatty acid, γ-linolenic acid, can support plasma AA levels as well as preformed AA (7, 8).

## Accretion in the growing foetus and infant

Considerable amounts of AA and DHA are deposited in the human brain and other tissues during intrauterine and postnatal growth (9). Dietary DHA increases brain DHA *in utero* and after birth more efficiently than its dietary precursor α-linolenic acid in humans and in primates (10–12). Foetal and infant brain DHA content is more affected by diet than AA content (10, 11). On average, the third trimester foetus accumulates an estimated 40 to 60 mg n-3 LC-PUFA per kg body weight per day (9). Regardless of the gestational age at birth, there is considerable interindividual variation in measured brain DHA content among human newborns. The variability may be due to differences in fatty acid supply or metabolism, other factors that influence intrauterine development as well as methodological limitations. Compared with term infants, preterm infants are at higher risk for inadequate LC-PUFA accumulation due to the interruption of the placental supply (13, 14). It appears prudent that postnatal feeding of preterm infants should aim at approaching intrauterine accretion rates of LC-PUFA.

## LC-PUFA in pregnancy

It is postulated that pregnancy increases the demand for LC-PUFA due to the needs for foetal growth and expansion of maternal tissues. Potential sources for foetal LC-PUFA accretion include maternal body stores, diet during pregnancy, and endogenous LC-

PUFA synthesis from the nutritionally essential fatty acids. There is a preferential materno-foetal transfer of LC-PUFA compared with the transfer of precursor essential fatty acids (15–17). Studies show a 3- to 4-fold variation in maternal LC-PUFA status among women in the same population, and maternal LC-PUFA status affects the LC-PUFA status of the newborn infant (18). In one intervention study, an increased supply of dietary n-3 LC-PUFA resulted in a small increase in duration of gestation and infant birthweight that was considered beneficial (19), but this was not confirmed in another study (20).

## LC-PUFA in lactation

Human milk provides AA, DHA and other LC-PUFA to breastfed infants, and consequently the maternal demand for LC-PUFA is increased by lactation. The fatty acid concentration of milk is related to the maternal diet and maternal plasma fatty acid composition, milk fat concentration, duration of breastfeeding and other factors (2, 21–23). An estimated 30% of human milk fatty acids are derived directly from the maternal diet, whereas the major portion is derived from the mother's body stores (24). Human milk DHA content is more variable, and the influence of dietary intake on milk content is greater than observed with AA (2).

## Physiological effects and animal studies

LC-PUFA have important effects on membrane function, photoreceptor differentiation, activation of the visual pigment rhodopsin, the activity of several enzymes, the function of ion channels, and the levels and metabolism of neurotransmitters and eicosanoids (25, 26). In non-human primates, low accumulation of retinal and brain DHA leads to abnormal retinal physiology, poorer visual acuity, longer duration of visual fixation, and increases in stereotyped behaviours and locomotor activity (27, 28).

## LC-PUFA and visual function

There are considerable data available from clinical studies in preterm and term infants. Some non-randomized studies comparing breastfed and formula-fed infants found an enhanced development of visual function in breastfed babies and a positive relation between duration of breastfeeding and visual acuity (29, 30), but these studies alone cannot provide conclusive evidence for a causal role of n-3 LC-PUFA. In preterm infants, several randomized, controlled clinical studies found that infant formula with DHA improves retinal function and visual acuity in the first postnatal months (31). Moreover, visual function correlated with DHA levels in the blood phospholipids suggesting that

some supplemented infants could have benefited from a higher level of supplementation (32). Dietary α-linolenic acid does not substitute for DHA with respect to visual function in preterm infants (31). In healthy, term infants, some randomized, controlled trials showed that DHA improved visual acuity during the first year of life, although others found no appreciable effect, but none reported negative effects on visual acuity (33). Differences among the results of various studies may be due to differences in methodologies, strategies of supplementation, and other variables.

## Effects of LC-PUFA on behavioural development

A few randomized studies have examined the effects of postnatal dietary LC-PUFA on global developmental tests or on specific measures such as visual attention, problem-solving and language. Some published studies of visual attention, problem-solving and global development found enhanced development in infants fed LC-PUFA (34–38), others found no effects (39), but one study reported poorer results on a measure of language development in infants receiving DHA without AA (40). The most consistent finding, and one supported by analogous data in non-human primates, has been longer fixation duration in infants with poorer n-3 LC-PUFA status, a result that may reflect less mature visual attention (34, 41). No negative effects on development have been observed with formulas containing both DHA and AA (39, 42, 43). Very little information is available on other important aspects of infant behaviour or on longer-term outcomes.

## Effects of LC-PUFA on other aspects of development

There is a paucity of data on the effects of dietary LC-PUFA on the development of the respiratory, digestive and immune systems in early childhood.

## LC-PUFA in dietary products for infants

LC-PUFAs in formulas and other dietary products enhance LC-PUFA levels in infants' plasma and tissue lipids. This biochemical effect can extend for months beyond the period of consumption (44, 45). A balanced supply of dietary AA and DHA in reasonable amounts and with adequate antioxidant protection has not led to poor growth or other adverse effects (39, 46, 47). High eicosapentaenoic acid (EPA) intakes are not desirable for infant feeding (48), but there is no concern about modest intakes of EPA, such as those found in human milk. All products and ingredients used for infant feeding need to be fully characterized with regard to safety.

## Recommendations for LC-PUFA supply to infants

Breastfeeding, which supplies preformed LC-PUFA, is the preferred method of feeding for healthy infants and is strongly supported. Infant formulas for term infants should contain at least 0.2% of total fatty acids as DHA and 0.35% as AA. These levels seem prudent given that they are at the lower end of the range of human milk DHA content world-wide. In recognition of the fact that preterm infants are born with much less total body DHA and AA than term infants, formulas for preterm infants should include at least 0.35% DHA and 0.4% AA. Higher levels than these might confer additional benefits and should be studied, as optimal dietary intakes for term and preterm infants remain to be defined.

## Recommendations for LC-PUFA for pregnant and lactating women

In the absence of published studies showing direct functional benefits of supplementation of LC-PUFA, the working group felt it was premature to recommend specific LC-PUFA intakes for pregnant and lactating women. The variability in LC-PUFA status among pregnant women is large, and studies to determine if the variability is related to functions in either the mother or infant are lacking. In the meantime, it seems prudent for pregnant and lactating women to include some food sources of DHA in their diet in view of the assumed increase in LC-PUFA demand in these physiological conditions and the relationship between maternal and foetal DHA status.

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