Chapter

Cytokines and Maternal Omega-3 LCPUFAs Supplementation

Yessica Rodriguez-Santana and Luis Peña-Quintana

Abstract

Daily supplementation of maternal diet during pregnancy and lactation with a fish oil-enriched dairy product increases the percentage of DHA and other omega-3 (ω-3) long-chain polyunsaturated fatty acids (LCPUFAs) in mothers (placenta, plasma, erythrocyte membranes, and breast milk) and children (plasma and erythrocyte membranes). This supplementation during critical periods such as pregnancy, lactation, and early development of a newborn may influence the levels of certain inflammatory cytokines, reducing pro-inflammatory cytokines and promoting an anti-inflammatory "environment". In pregnant women who have not received any supplement of omega-3 LCPUFAs, IL-6 plasma levels are higher, while TNF-alpha plasma levels are also higher in their breastfed infant at birth and 2 months thereafter. There could be a relationship between docosahexaenoic acid (DHA) and the concentrations of different cytokines.

Keywords: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), omega-3 LCPUFAs, pregnancy, lactation, cytokines, fatty acids

1. Introduction

Interest in the therapeutic effects of omega-3 (ω-3) fatty acids has grown over the last 30 years, particularly in regard to visual and neurological development in newborns, the immune system, and inflammatory and cardiovascular diseases [1–9].

Inflammation is one of the principal causes of complications during pregnancy and of prematurity and neonatal morbidity [10–15].

Docosahexaenoic acid (DHA) has anti-inflammatory effects and can alter the production of inflammatory cytokines in animal models, cell culture, and in humans [16–26]. A high intake of omega-3 fatty acids has been associated with a reduction in arachidonic acid-derived inflammatory eicosanoids, cytokine production, reactive oxygen species, and expression of adhesion molecules [27]. It is also associated with the production of lipid mediators [28] that have anti-inflammatory [29–31] and immunomodulatory effects [27]. Both eicosapentaenoic acid (EPA) and DHA affect the function of many immune cells and can have a beneficial effect in preventing inflammatory or immune-mediated diseases, but their effects and mechanisms of action can differ [32]. They can inhibit the production of pro-inflammatory cytokines such as tumour necrosis factor-alpha and interleukin (IL)-1 and IL-6 [33]. In animal models their intake during pregnancy appears to exert an anti-inflammatory effect on damaged tissue in the young [34–36], while in humans it produces a decrease in Th1 cytokines such as interferon-gamma (IFN-γ)

and IL-1 in infants' plasma and a decrease in the Th2 cytokines IL-14 and IL-13 in the umbilical cord blood [32, 37].

2. Omega-3 fatty acids

Long-chain polyunsaturated fatty acids are fatty acids containing at least 18–20 carbon atoms. They are categorised into two main families according to the position of the first double bond [38], as either omega-3 series or omega-6 series. In omega-3 fatty acids, the first double bond is between the third and fourth carbon atoms (**Table 1**).

The most relevant omega-3 LCPUFAs are alpha-linolenic acid (ALA), docosahexaenoic acid, eicosapentaenoic acid, and docosapentaenoic acid (DPA), while the most relevant omega-6 LCPUFAs are linoleic acid (LA) and arachidonic acid (ARA).

2.1 Synthesis and sources of fatty acids

In humans, the synthesis of omega-3 and omega-6 fatty acids is limited; they are therefore considered essential fatty acids. LA and ALA are synthesised in large quantities in plants, but humans and other mammals cannot make them from their precursor, oleic acid, because they lack the active enzymes Δ-12 and Δ-15 desaturase [38]. Humans can synthesise other long-chain fatty acids such as ARA, DHA, and EPA from LA and ALA, which are precursors to the omega-6 and omega-3 series, respectively. However, conversion of these fatty acids to DHA, EPA, and ARA is inefficient [39], the most efficient method being to obtain them from the diet. Conversion can vary between sexes and is more efficient in women [40]. It increases during pregnancy and is reduced in newborns [40] due to their lower enzymatic activity.

Both omega-3 and omega-6 LCPUFA syntheses occur via the same pathway of elongation, desaturation, and peroxisomal retroconversion [41]. The most important enzymes in the desaturation processes are Δ-5 and Δ-6 desaturase. The two precursors, LA and ALA, compete for Δ-6 desaturase, but the enzyme has a greater affinity for ALA [40]. Therefore, a high supply of ALA causes a reduction in the synthesis of LA derivatives. In contrast, if LA supply is greater than ALA supply, conversion of ALA to its derivatives is limited. The Western diet contains 10–20 times more omega-6 than omega-3 fatty acids [41]. In addition, the fatty acid content of plasma and many other tissues comprises predominantly omega-6 fatty acids, with the exception of the brain and retina, which are rich in omega-3 [41]. Thus, a high intake of EPA and DHA results in a decrease in tissue levels of ARA and an increase in EPA and DHA, due to enzymatic competition between the two series [42].

Omega-6 fatty acids	Linoleic acid (LA) C18:2 ω-6
	Arachidonic acid (ARA) C20:4ω-6
Omega-3 fatty acids	Alpha linolenic acid (ALA) C18:3 ω-3
	Eicosapentaenoic acid (EPA) C20:5 ω-3
	Docosahexaenoic acid (DHA) C22:6 ω-3
	Docosapentaenoic acid (DPA) C22:5 ω-3

Table 1.
Omega-6 and omega-3 long-chain polyunsaturated fatty acids.

Polyunsaturated fatty acids are found mainly in oily fish and in seed oils. LA, the precursor of omega-6 fatty acids, is present in soybean, corn, and sunflower oils, while ALA, the precursor to omega-3 fatty acids, is found in numerous vegetables, such as linseed, canola, pumpkin seeds, and walnuts. The main dietary sources of EPA and DHA are cold-water oily fish (e.g. sardines, salmon, mackerel, and herring) [43] (**Figure 1**).

Despite the benefits of a diet rich in omega-3 fatty acids, there is no consensus on their recommended daily intake. The dietary recommendations from national and international bodies on the intake of omega-3 long-chain fatty acids, in particular EPA and DHA, vary between 200 and 600 mg per day for adults and 40 and 250 mg per day for infants older than 6 months, children, and adolescents [42]. These recommendations are based on the observed association between the omega-3 fatty acid consumption and reduced risk of cardiovascular disease. According to the Nutrition Committee of American Heart Association (AHA Nutrition Committee) recommendations, eating at least two servings of fish per week or 500 mg per day of omega-3 LCPUFAs prevents and reduces the risk of cardiac disease [44, 45]. The expert panel of the European Food Safety Authority (EFSA) recommends an intake of 250 mg per day of omega-3 LCPUFAs, in contrast to the Australian suggested dietary targets of 610 mg EPA and 430 mg DHA per day in adults to reduce cardiovascular risk [38, 46, 47]. To achieve an anti-inflammatory effect, it is recommended to eat between 500 and 1000 mg of omega-3 fatty acids per day [48]. There are also specific recommendations for certain population groups: in pregnant or breastfeeding women, an additional intake of 100–200 mg DHA per day is recommended to compensate for oxidative losses of DHA and its accumulation in the foetus [42].

Figure 1.
LCPUFAs food sources.

There are few data on the adverse effects of long-term high-dose DHA supplementation. The EFSA expert panel considers DHA dietary supplementation of up to 1 g per day to not pose a risk in the general population. In a systematic review [1] of studies on DHA supplements during pregnancy, it was concluded that an intake of 1–2.7 g per day of omega-3 LCPUFAs is not harmful.

2.2 General functions of fatty acids

2.2.1 Cell membrane structure and function

Omega-3 polyunsaturated fatty acids are important structural components of cell membranes, where they are present as membrane phospholipids (esterified fatty acids) or as free molecules [49]. The incorporation of free polyunsaturated fatty acids into membrane phospholipids appears to alter the physical properties of the membranes. They can influence the structure of membrane phospholipids, reducing the van der Waals interactions [50].

They contribute to several membrane functions such as fluidity, permeability, enzymatic and receptor activity, gene expression, and signal transduction [41, 42, 51]. The changes in permeability appear to depend directly on the degree of fatty acid desaturation [49]. EPA and DHA are of particular biological importance.

2.2.2 Visual and neurological function

The nervous system takes a long time to develop and mature, but there are many crucial events that occur during pregnancy and the first years of life. The brain grows rapidly between week 20 of gestation and 2 years of age, increasing in size by 64% during the first 3 months of life [52]. In these stages there is a period termed the *window of sensitivity*, during which certain nutrients or stimuli can influence and promote neurological development and functional brain capacity. Several nutrients have been described to play a crucial role in the development of the nervous system, including choline, iron, zinc, and long-chain fatty acids such as nervonic acid and DHA [53–55].

DHA forms part of the structural lipids of cell membranes, particularly the phospholipids found in the nervous tissue and the retina [38], where high levels of DHA have been found, primarily in the grey matter and photoreceptors; it is therefore thought to be essential for proper neurological and visual development [9, 35, 56–58]. Similarly, high levels of omega-3 polyunsaturated fatty acids have been found in the basal ganglia, frontal cortex, occipital cortex, hippocampus, and thalamus in studies performed on the young of baboons and rats, which suggests that they affect sensory-motor integration and memory [59–61]. Cerebral development affects cognitive, social, and motor functions and communication. Stimulation and optimal nutrition [62] are essential. It has been demonstrated that babies who receive adequate quantities of omega-3 LCPUFAs, especially of DHA, show better development in these areas [63–68], so DHA is thought to be essential for the growth and function of neuronal and visual tissue [53]. These benefits continue beyond childhood [64, 69], and DHA is recommended as an essential dietary component in breastfeeding women and in children, to support brain development [54].

DHA appears to have important properties as a free radical scavenger, protecting against oxidative damage in developing and adult brains. It also has a role in neuronal plasticity, a process that allows the replacement of damaged neuronal circuits and reorganisation of existing ones. It combines with glycerophosphocholine and phosphatidylserine to promote the formation of membrane phospholipids for the growth of nerve cells [55] and has also been observed to play a role in cell

migration during brain development [70]. Animal studies have demonstrated that DHA supplementation during pregnancy and breastfeeding is associated with an increased density of dendritic spines in the hippocampus [71] and of some synaptic proteins in the brains of weaned rats, while DHA deficiency has been associated with smaller neuronal soma [72] and altered synaptic vesicle density and neuronal growth and survival. Another study has demonstrated that supplementation with DHA significantly increases neuronal growth and synaptogenesis and increases levels of pre- and postsynaptic proteins involved in synaptic transmission and long-term potentiation, which is associated with improved synaptic function [73].

2.2.3 DHA and oxidative stress

Omega-3 fatty acids are considered effective in the prevention of many diseases due to their antioxidant effects [74], yet there remains some debate on the subject. DHA, being a highly unsaturated fatty acid, is extremely susceptible to lipid peroxidation. Therefore, it is essential to ensure that LCPUFA supplements are safe, as they may generate free radicals that can affect the tissues. However, several studies in children found no abnormalities in baseline levels of peroxidised lipids nor in antioxidant enzymatic activity. Randomised studies in which up to 1 g per day of DHA or 2–7 g per day of omega-3 LCPUFAs was given found no adverse effects, including in pregnant women [75, 76].

Pregnancy is a state in which there is a high metabolic demand and increased production of free radicals. Pregnant women have been observed to have higher levels of free radical damage than non-pregnant women. Labour also involves increased oxidative damage in both mother and baby, being even higher in premature newborns [77, 78]. Studies carried out in animals have found increased activity of superoxide dismutase (SOD), an important antioxidant enzyme, in rat brains following post-natal DHA supplementation [79]. In a subsequent study in pregnant women, it was suggested that consumption of fish oil during pregnancy could have antioxidant effects during this period although the results were not conclusive [80].

2.2.4 Other benefits and disease prevention

Several studies have demonstrated the beneficial effect of fatty acids in inflammatory [81, 82] and autoimmune diseases such as systemic lupus erythematosus [43], asthma, cystic fibrosis [83], chronic obstructive pulmonary disease (COPD) [38], rheumatoid arthritis [81], multiple sclerosis [33, 38, 84, 85], ulcerative colitis [86], Crohn's disease [81], and type 2 diabetes mellitus [33, 87].

The beneficial effects of omega-3 fatty acids on cardiovascular disease are widely known [88, 89]. Omega-3 LCPUFAs not only reduce triglyceride levels [90–93] but also reduce the production of chemotactic agents, growth factors, adhesion molecules, inflammatory eicosanoids and inflammatory cytokines, decrease blood pressure, increase nitric oxide production, improve endothelial relaxation and vascular compliance, and reduce thrombus formation and cardiac arrhythmias [94, 95]. Although the mechanisms of their protective effects are not fully established, it has been proposed that they may be due to the anti-inflammatory effects of these fatty acids on blood vessel walls [95], their aforementioned lipid-lowering effect, the regulated production of less potent eicosanoids, and the inhibition of pro-inflammatory cytokine production [89, 94], mechanisms which have also been shown to exert benefits in peripheral vascular disease [94].

Fish oil supplementation has also been shown to be beneficial in oncological processes [38] and is associated with a reduced incidence of metastatic breast cancer [33]. Its benefits have also been demonstrated in patients with colorectal

cancer [96], with an observed reduction in inflammatory markers such as interleukin-6 (IL-6) in patients taking omega-3 fatty acid supplements, although these benefits are dependent on the duration, dose, and route of supplementation and the specific type of oncological treatment received. Its effects in leukaemia, lymphoma, neuroblastoma, glioblastoma, and lung, cervical, pancreatic, bladder, and ovarian cancer [97] have also been studied. The proposed mechanisms by which LCPUFAs act as adjuvants in cancer-specific treatments relate to their antitumour properties: they are anti-inflammatory [98], antiproliferative, pro-apoptotic, anti-invasive, and antimetastatic [99] and have epigenetic-regulatory effects [100]. Further studies are required to establish the therapeutic recommendations for EPA and DHA in oncological processes [97].

3. DHA and inflammation

Inflammation is part of the body's normal response to injury or infection. However, when it is uncontrolled or inappropriate, it can damage the body's own tissues, contributing to a wide variety of chronic and acute disorders. Inflammation is characterised by the production of inflammatory cytokines, ARA-derived eicosanoids (prostaglandins, thromboxanes, leukotrienes), reactive oxygen species (ROS), and molecular adhesion [81, 101].

The term *cytokine* encompasses a group of families of low molecular weight molecules that are structurally related and comprise more than 200 members. They are characterised by their ability to alter the functional activity of cells and tissues [102]. They are involved in the immunoregulatory and effector mechanisms of the innate and adaptive immune system. They are also involved in angiogenesis and have been found to play a key role in neuro-immune and neuroendocrine processes. Their pleiotropism makes their functional classification difficult, but they can be divided according to their most significant function into the following groups [103, 104]: adaptive immune mediators, innate immune mediators, haemopoiesis mediators, and pro-inflammatory and immunosuppressive cytokines.

In disease states, fish oil has been shown to act as an anti-inflammatory agent. Omega-3 fatty acids regulate the production of ARA-derived eicosanoids [81]. EPA competes with ARA to stimulate the production of series three prostaglandins and series five leukotrienes that have a lesser inflammatory action than ARA-derived eicosanoids. Supplementation with DHA leads to changes in the metabolism of ARA and in the balance of eicosanoids synthesised from omega-3 and omega-6 fatty acids. Thus it can affect the functions regulated by these eicosanoids [42].

Although fatty acids can modify the quantity and type of eicosanoids produced, they can also modify inflammation via eicosanoid-independent mechanisms that include acting on receptors, intracellular signalling pathways, and transcription factor activity [51]. They are able to reduce levels of C-reactive protein (CRP), cytokines [81], chemokines, and other inflammatory biomarkers. In addition, they produce the lipid mediators known as resolvins and protectins, which have anti-inflammatory and immunomodulatory effects [27–30, 43, 81]. Other anti-inflammatory actions of omega-3 LCPUFAs include a reduction in major histocompatibility complex (MHC) class II antigen presentation, reduction in reactive T cells, and reduction in Th1 cytokine production.

Omega-3 LCPUFAs could be said to act directly on inflammation by replacing arachidonic acid as a substrate for eicosanoid synthesis and indirectly by altering the expression of inflammatory genes via activation of transcription factors [101], among other mechanisms. The pathways are complex and much remains to be determined. It is thought that the nuclear factor (erythroid-derived 2)-like 2 (Nrf2)

transcription factor plays a key role in the anti-inflammatory effects of DHA and EPA. Via Nrf2-dependent signalling, DHA can inhibit pro-inflammatory mediators such as nitric oxide synthase and cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines such as IL-6, interleukin-1 (IL-1), and tumour necrosis factor-α (TNF-α) [33]. Other studies suggest that omega-3 LCPUFAs are natural ligands of peroxisome proliferator-activated receptor gamma (PPAR-γ), a transcription factor that regulates the expression of genes involved in cellular proliferation, inflammation, and metabolism of fatty acids and lipoproteins. Activation of PPAR-γ can inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling and expression of inflammatory genes [105]. Despite the available data, little is known about the cellular and molecular mechanisms by which omega-3 LCPUFAs exert their beneficial effect in the prevention of inflammatory and immune diseases [32]; such mechanisms are yet to be fully determined.

4. DHA in pregnancy and lactation

Essential fatty acids and those derived from LA (the omega-6 group) and ALA (the omega-3 group) play an important role during pregnancy. They have been associated with prolonged pregnancy, delay of spontaneous labour and reduction in recurrent premature labour in animal and human studies, improving neonatal outcomes [106]. In vulnerable states such as pregnancy and lactation, a high intake of omega-3 LCPUFAs is recommended as maternal levels of DHA decrease during pregnancy [1] and continue to decrease if the lactation period is long [107]. Maternal DHA levels have also been observed to decrease further in multiple pregnancies and are lower in multiparous than in primiparous women [108] and when the time between pregnancies is short. This could be explained by the high demand for these fatty acids during pregnancy as the foetus receives them preferentially via the placenta [109]. The foetus' DHA status depends exclusively on this transfer and in turn its supply in the mother's diet [110]. Indeed, omega-3 PUFA supplementation in pregnancy has been associated with increased DHA concentrations in the plasma, placenta, and umbilical cord blood [111].

Lactation is another period in which DHA consumption is beneficial for both the mother and child. Breast milk contains DHA, as well as omega-6 and other omega-3 LCPUFAs, which make up 2% of the total fatty acid content. It also contains components that play a specific immunological role such as cytokines, growth factors, leucocytes, immunoglobulins, lysosomes, and proteins such as lactoferrin. The presence of cytokines in breast milk helps the neonatal immune system develop and confers protection to the infant who does not yet have a network of mature cytokines [112]. Even at femtomolar concentrations, they can regulate the actions and properties of immune cells. A wide range of both pro-inflammatory and anti-inflammatory cytokines has been detected via numerous methods in breast milk throughout the different stages of lactation and includes IL-1 beta (β), IL-6, TNF-α, and transforming growth factor beta (TGF-β) [113].

The fatty acids present in breast milk also appear to play an important role in the maturation and function of the immune system. Exclusive breastfeeding for the first few months of life has been demonstrated to protect not only against various types of infection (respiratory, gastrointestinal, urinary, otitis media, and necrotising enterocolitis) [114, 115] but also against allergic diseases. For this reason, and others, breast milk is the ideal foodstuff for the newborn [116] as it provides the nutrients necessary for optimal growth and development. The composition of polyunsaturated fatty acids in breast milk is determined partly by the dietary PUFA content. There is a correlation between breast milk DHA levels and blood levels.

Likewise, there is a correlation between breast milk DHA levels and infant plasma levels [117, 118]. Other studies on supplementation have found a positive association between fish oil supplementation and a reduced plasma ω6/ω3 ratio in maternal plasma and in umbilical cord blood [119].

A dietary supply comprising mainly omega-6 fatty acids, as occurs in Western diets, can significantly inhibit the endogenous synthesis of omega-3 fatty acids, especially EPA and DHA given the enzymatic competition between their precursors. This becomes particularly relevant in the developing foetus and newborn, especially in premature or small-for-gestational-age babies [9]. Due to the limited capacity for synthesising these fatty acids [58], neonates are exclusively dependent on their placental transfer during pregnancy and their supply from breast milk. Therefore, a limited intake of omega-3 fatty acids in pregnancy or lactation can be associated with insufficient DHA levels for optimal neurological and immunological development in the foetus and newborn. In these states, a preventative nutritional intervention becomes particularly relevant as the fat that the mother consumes during pregnancy and lactation will greatly influence both foetal development and the lipid composition of breast milk and in turn the newborn's nutrition during the first stages of life [76, 120].

5. Patients and methods

We studied whether supplementing maternal diet with omega-3 LCPUFAs during the last trimester of pregnancy and the breastfeeding period influenced the levels of inflammatory cytokines in mother and child. Our study included a group of healthy infants born to term to 46 mothers, who had been enrolled in a registered, double-blind controlled randomised trial, from week 28 of pregnancy to the fourth month of lactation. Mothers were recruited in the Services of Gynecology of the Mother and Child Hospital of Granada, Spain (Hospital Materno-Infantil de Granada), and the Mother and Child University Hospital of Las Palmas de Gran Canaria, Spain (Complejo Hospitalario Universitario Insular Materno-Infantil de Canarias), between June 2009 and August 2010. Our sample was taken from an earlier larger study designed to assess the effects of omega-3 LCPUFA supplementation on the fatty acid profile of mothers and newborns [121]. The earlier study was registered on www.clinicaltrials.gov under identification code NCT01947426. The experimental groups were fish oil (FO) group (n = 24) which received 400 ml of fish oil-enriched drink [320 mg DHA + 72 mg EPA] per day and control (CT) group (n = 22) which received 400 ml of a non-supplemented drink per day. The dairy drinks were not commercially available products but specifically prepared for the study. The dietary supplementation started on week 28 of pregnancy and finished on the fourth month of lactation. We determined in mother and children plasma the concentrations of the following cytokines: GM-CSF, IL-2, IL-4, IL-6, IL-10, INF-γ, and TNF-α using MILLIPLEX® Human Cytokine/Chemokine kit in conjunction with a Luminex 200® system (Austin, TX, USA) and xPONENT® software package. The fatty acid profiles of maternal and children compartments were analysed in an earlier study [121], and DHA levels in mother and children plasma and erythrocyte membranes, as well as in breast milk, were used to evaluate correlation with cytokine levels.

6. Omega-3 fatty acids and cytokines during pregnancy

Supplementation with omega-3 LCPUFAs during pregnancy affects the pattern of fatty acids in maternal plasma and umbilical cord blood [122–124].

Supplementation increases DHA levels not only in these compartments but also in breast milk and in the infant's plasma if they are breastfed [121, 125].

Inflammation is considered one of the main causes of complications during pregnancy and of prematurity and neonatal morbidity [10–15]. Indeed, pregnancy may be considered a mild, controlled, systemic inflammatory state. Cytokines TNF-α and IL-1 are heavily involved in the inflammatory processes associated with pregnancy and labour [10, 12, 13], although an increase in inflammatory biomarkers such as IL-8, hepatocyte growth factor and monocyte chemotactic protein during pregnancy have also been demonstrated. There is also a progressive increase in vascular biomarkers, such as E-Selectin, vascular adhesion molecule 1, intercellular adhesion molecule (ICAM) 1, and plasminogen activator-inhibitor 1 [126]. Other studies have suggested that an abnormal response from cytokines and other molecules such as leptin may be involved in the pathophysiology of pregnancy-related complications such as preeclampsia. An association has been demonstrated between TNF-α, IL-6, IL-8, IL-10, and leptin, indicating that a rise in these markers could be used as a marker of inflammatory dysfunction and endothelial dysfunction in preeclampsia [103]. In women with a diagnosis of preeclampsia, increased levels of inflammatory cytokines such as IL-6 have even been found in breast milk [104].

Significant changes can also take place during pregnancy that affect lipid and carbohydrate metabolic pathways and vascular function. Adipose tissue acts as both a store of energy during pregnancy and a metabolically active tissue [126]. Adipocytes and their stroma are a rich source of cytokines and inflammatory mediators such as TNF-α and adiponectin, which increase and decrease insulin resistance, respectively [127]. The increased insulin resistance and the changes that occur in the maternal lipid profile during pregnancy could play an important role in endothelial dysfunction [128]. The role of adipokines, cytokines, and vascular homeostasis biomarkers in the regulation of metabolic changes during pregnancy remains to be fully established. There are a few studies, some of which are in animal models, that have investigated the effect on inflammation of omega-3 LCPUFA supplementation during pregnancy [34–36, 126, 129, 130].

A high intake of omega-3 fatty acids has been demonstrated to reduce the production of eicosanoids, cytokines, ROS and expression of adhesion molecules. Cell culture studies [33] have reported that EPA and DHA can inhibit the production of pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, and in vitro studies have demonstrated that they can also reduce the expression of cell adhesion molecules and recently also in endothelial cells of the umbilical cord. These effects are supported by similar studies on dietary supplementation in animal and human models. In animal models, a reduction in the inflammatory response, expression of remodelling enzymes, and functional improvement has been demonstrated in offspring exposed to stressful situations whose mothers received DHA during pregnancy [34, 35]. In humans, some studies have revealed a decrease in cytokine levels, as a measure of systemic inflammatory response, after 8 weeks of fish oil supplementation [23]. During pregnancy, it has been demonstrated that intake of omega-3 long-chain fatty acids can modify cytokine levels and maturation of helper T (Th) cells [32]. Comparative studies in breastfed children whose mothers received EPA and DHA supplements from week 22 of pregnancy showed that this dietary intervention confers a reduction in Th1 cytokines such as IFN-gamma and IL-1 in the plasma and a reduction in the Th2 cytokines IL-14 and IL-13 in the umbilical cord blood [37]. In our study, in which mothers received supplements from week 28 of pregnancy and throughout breastfeeding, we found that levels of IL-6, TNF-α, IL-4, and IL-10 could be altered [26]. Maternal plasmatic levels of IL-10 and IL-4 were higher in the supplemental group (FO) than in the control group (CT). On the other hand, plasmatic IL-6 levels were higher both in mothers and children of the

CT group. Additionally, TNF-α was higher in CT children [26]. In a study on depression in pregnant women, it was also observed that prenatal EPA supplementation in particular reduced maternal levels of IL-6, Il-15, and TNF-α [131]. Clinically, these findings could translate to an increased anti-inflammatory "environment" provided by omega-3 LCPUFAs. TNF-α and IL-6 are pro-inflammatory, and IL-10, although it has both effects [131, 132], is considered the principal regulator of T cells and may act as an anti-inflammatory mediator of omega-3 LCPUFAs [133]. However, some studies have found no correlation between DHA and different cytokines: a study by Hawkes et al. [129] found that women receiving supplementation during pregnancy with a combination of 600 mg DHA plus 140 mg EPA daily for 4 weeks had an increase in omega-3 LCPUFA levels in the cells studied. DHA levels increased in a dose-dependent manner in the plasma and breast milk, which highlights the benefits of this dietary intervention. However, no significant differences were found between groups in the production of cytokines, either in breast milk cells or in peripheral blood. In addition to the dose, the duration of supplementation could be the key.

There has been some investigation into the clinical effect that supplementation may have on infants [133–136]. It has been observed that increased dietary intake of salmon during pregnancy increases levels of omega-3 LCPUFAs in umbilical cord plasma and affects cytokine production in neonates, with lower levels of IL-2, IL-4, IL-5, IL-10, and TNF-α in response to various stimuli [133]. Reduced IL-10 production has also been observed in vitro following stimulation with cat allergens in an atopic population [134]. Increased DHA and EPA in mother and child results in lower levels of PGE-2, a pro-inflammatory eicosanoid and inducer of IL-10 production, which could explain the reduced secretion of IL-10 in these individuals. This concept is also supported by Warstedt et al. [136] who suggested that reduced maternal levels of PGE-2 after omega-3 LCPUFA supplementation could contribute to a foetal immune system less prone to developing inflammatory disease such as allergies, since eicosanoids, cytokines, and chemokines are closely associated with the immune response. However, although results have been promising, it is still unclear whether or not omega-3 LCPUFAs affect the development of atopy [4].

Changes in fatty acid levels have been demonstrated to affect cytokine levels. A positive association has been observed between DHA and IL-10 such that at higher concentrations of DHA, IL-10 secretion is increased [26, 131]. Likewise, DHA has been negatively associated with IL-6, which could translate to an increased anti-inflammatory effect [26, 137]. These findings will need to be confirmed in future studies to clarify the uncertainties regarding the various mechanisms by which omega-3 LCPUFAs can affect inflammatory cytokines [137].

7. Conclusions

DHA supplementation during the third trimester of pregnancy and during breastfeeding can affect cytokine production, increasing anti-inflammatory cytokine levels and decreasing pro-inflammatory cytokine levels. These effects may translate to a lower risk of pregnancy-related complications and childhood disease, but much remains to be investigated in these fields.

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Conflict of interest

The authors declare no conflict of interest.

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