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II Consensus of the Brazilian Nutrology Association on DHA recommendations during pregnancy, lactation and childhood

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Abstract

Objective: To update of the consensus of the Brazilian Association of Nutrology regarding DHA consumption and supplementation during pregnancy, lactation and childhood. **Methods:** Scientific articles published until 2022 were reviewed in Pubmed/Medline, SciELO and Lilacs databases. **Results:** Considering the information obtained, the authors drafted the consensus, which was approved by the Brazilian Association of Nutrology board. **Conclusions:** The recommendations of the Brazilian Nutrology Association are presented based on scientific evidence.

Keywords: DHA. Ômega 3. Consensus. Pregnancy. Lactation. Children. LCPUFAS.

Introduction

In nutrition science, research always highlights new approaches and the need to review nutritional recommendations on energy, macro and micronutrients. The general definitions for lipids, among them polyunsaturated fatty acids (PUFAS) with long chains (above 18 carbon atoms) and at least two double bonds in their chemical structure, have been frequently revisited in literature. PUFAS can be divided into two major groups: the omega-6 (ω-6) fatty acid (FA) family and the omega-3 (ω-3) fatty acid (FA) family. Fatty acids are carboxylic acids of long acyclic hydrocarbons chains, non-polar and without branches. They are classified according to the number of carbons in the chain, the number of double bonds and the position of the first double bond in the carbon chain. Saturated fatty acids are those that do not have double bonds, while monounsaturated FA have one double bond, and polyunsaturated FA have more than one double bond **[1]**. The ω-3 series FA have a chemical structure formed by carbon and oxygen units joined by single or double covalent chemical bonds. The degree of unsaturation maintains a direct relationship with the number of double bonds, and all ω-3 have the first double bond located in the third carbon from the terminal methyl group **[2]**. The important omega-3 fatty acids for humans are linolenic acid, eicosapentaenoic acid (EPA) and docosaexaenoic acid (DHA).

Docosahexaenoic acid, known as DHA, is conditionally essential, meaning it is not produced by the human body in sufficient quantities. It is part of the ω-3 AG family and its chemical structure is composed of a chain of 22 carbon atoms (C22) with 6 double bonds (22:6n-3 - all-cis-4,7,10,13,16,19-docosahexaenoic acid) **[2]**. Eicosapentaenoic acid (EPA) is also in the ω-3 AG group, composed of 20 carbon atoms (C20) and 5 double bonds (20:5n-3 - all-cis-5,8,11,14,17-eicosapentaenoic acid) **[3]**. Alpha linolenic acid (ALA)

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has 18 carbon atoms (C18) in the hydrocarbon chain, and its first double bond is in the third carbon (18:3n-3 - all-cis-9,12,15-octadecatrienoic acid) **[3]**. ALA is an essential fatty acid, meaning it is not synthesized by the human body. It plays important roles in the structure of cell membranes and metabolic processes. In addition, it is a substrate for the synthesis of fatty acids of larger chains and with a greater number of double bonds, such as eicosapentaenoic acid, 20:5n-3 (EPA), and docosaexaenoic acid, 22:6n-3 (DHA) **[4]**. It is found in plant foods such as flaxseed, canola, soy and corn oils and nuts. EPA and DHA are found in marine fish such as tuna, salmon, mackerel and herring. Although, in humans, alpha-linolenic acid is converted into EPA and DHA, it is not known for sure which percentage is actually converted **[5]**, but it is estimated to be quite low **[6]**, of the order of 5% for EPA and 0.5% for DHA **[7]**. It is known that children, especially younger ones, due to their enzymatic immaturity, cannot convert all the DHA necessary for their development from alpha-linolenic acid **[8]**.

Importance of DHA

The biological role of animal origin ω-3 FAs has been well documented. As for the infant population, EPA and DHA fatty acids perform important biochemical and physiological functions for both metabolism and health. Also, DHA is a fundamental nutrient for the child's growth and development, which main role is in the formation and functioning of the central nervous system and retina **[9]**.

Epidemiological studies have pointed out the association of ω-3 PUFAs with maternal health during pregnancy and child health, in outcomes such as duration of pregnancy, premature birth, birth weight, peripartum depression, gestational hypertension / preeclampsia, patterns of postnatal growth, visual acuity, neurological development, cognitive development, autism spectrum disorder, ADHD, learning disorders, atopic dermatitis, allergies and respiratory disorders. It is important to highlight that some results have been contradictory and studies continue to be published in order for the best answers to be found **[9]**.

In pregnancy, supplementation with 150 to 1,200 mg of DHA per day may prolong pregnancy, increase birth weight and reduce the risk of preterm delivery **[10]**. Valentine et al. **[11]**, in a randomized double-blind clinical trial, suggests that DHA supplementation at a higher dose during pregnancy may contribute to immunomodulatory regulation through its influence on IL-6 levels and advanced glycation end products.

Meta analysis published in the Cochrane Library journal, in February 2020, evaluated the results of 86 randomized clinical trials involving 162,796 people. Those studies analyzed the possible effects of increased intake of omega-3 fats, based on marine fish and algae, on allcause mortality, cardiovascular events, adiposity and serum lipids. The sample consisted of adults, some with pre-existing diseases and others healthy, from North America, Europe, Australia and Asia. Most trials provided EPA and DHA in capsule, and few opted for marine fish. Regarding lipid profile, studies have confirmed that the consumption of EPA and DHA reduce triacyclglycerols levels by about 15%, although it does not have beneficial effects on serum concentrations of other lipids **[12]**.

Other scientific evidence shows that supplementation with 2 to 4 g/day of EPA and DHA may reduce plasma concentration of triacyclglycerols by between 25% and 30%, so supplementation with marine omega-3 (2-4 g/day) may be recommended for severe hypertriglyceridemia (> 500 mg/dL) as part of treatment, at medical discretion **[13]**. In the elderly population, a neuroprotective role with anti-inflammatory potential of omega-3, mainly EPA and DHA, has also been observed. These are of great importance in neurobiological processes, such as participation in the dynamic structure of cell membranes, transmission of nerve impulses, increased fluidity and serotonin transport. Moreover, they may be involved in maintaining cognitive function or preventing dementia, maintaining membrane integrity and neuronal function or through its antithrombotic and anti-inflammatory properties. They also act as synthesis inhibitors of pro-inflammatory mediators, such as cytokines; especially TNF-α and IL-1β **[14]**.

The most abundant omega-3 in brain cell membranes, about 30% of fatty components, are DHA molecules, and its main function is to provide synaptic fluidity and plasticity. These functions are the basis of memory mechanism, essential for the individual's cognitive ability, but oxidative stress, naturally caused by aging, promotes the reduction of DHA levels in the brain **[14]**.

Nutritional sources of DHA

A diversified diet with all the food groups is essential for maintaining a good health condition. DHA food sources are found mainly in marine fish and algae, and the amount of DHA can vary greatly in each species of fish, such as wild salmon, which is not available in Brazil. The salmon consumed in our country is from fish ponds and the fish DHA content depends on the consumption of DHA fortified feed **[15]**. In Brazil,

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sardines represent the main source of DHA of the diet, but its consumption still do not meet the recommendations. In addition, in contrast to the potential benefits that regular dietary intake of marine fish generates for health, certain chemical contaminants, such as heavy metals and chlorinated pesticides, may be present in fish commonly consumed **[14]**. It is important to note that evidence shows that fish consumed in Brazil contains low amounts of omega-3 **[16]**.

Another source of DHA is krill oil, a shrimp-like crustacean found in the South Seas. Krill oil is a unique source of EPA and DHA, as most ω-3 fatty acids are found in phospholipids. Izar et al, consider that krill ω-3 bioavailability is greater compared to marine ω-3 **[13]**. As for Yurk-Mauro et al, both bioavailabilitys are equal **[17]**. A recent source of DHA, widely used by vegan and vegetarian individuals, comes from microalgae. Studies show that DHA consumption of these algae significantly increased the concentration of DHA in plasma, serum, platelets and erythrocytes. As well, positive effects were observed in ω-3 rates in vegetarian and vegan populations **[18]**.

In a 100 g serving of fish (a small fillet), the following amounts of DHA are found (**Table 1**):

Table 1. Main nutritional sources of DHA.

Food	***mg DHA/100g food***
Abbot, fillet (grilled)	420
Tuna (canned in oil)	190
Corvina (cooked)	200
Lambari (fried)	230
Manjuba (fried)	1160
Hake (fried)	600
White hake (fried)	450
Salmon, with skin (grilled)	1220
Salmon, skinned (grilled)	750
Sardines (canned in oil)	460

Source: Brazilian Food Composition Table (TACO), 2011 **[19]**.

Nutritional status related to DHA in the Brazilian population

Brazil, despite having an extensive coastal region and favorable natural conditions, such as the favorable climate, does not occupy a prominent position, accounting for less than 1% of the world's production of fish **[20]**. Despite the growth in fish intake by the Brazilian population, per capita consumption is still considered low, an average of 9 kg/inhabitant/year, about 10 kg less compared to the world average, i.e., consumption is still below the minimum average established by the World Health Organization (WHO), of 12 kg of fish/inhabitant/year **[21]**.

The reasons for this fact may be: the high cost and access to the product, the difficulty in the distribution of fresh fish in most of the country, the lack of consumption combined with the preference for other types of meat, the low quality of the product found in free fairs and markets and the fact that the preparation of fish is considered difficult by the Brazilian population **[22,23]**. Thus, tax incentives, reducing the cost to the population, improved access to points of sale and dissemination of practical and simple recipes are measures to be implemented in public policies, aiming to increase the consumption of fish.

Brazilian study conducted by Lopes et al. **[22]** observed that the frequency of fish consumption by the Brazilian population remains low. While most participants reported consuming fish once or twice a month, few people have fish as a source of protein in their meals weekly, at least once. With regard to fish consumption by the child population, according to data from the IBGE National Continuous Household Sample Survey 2018 and fish consumption, children's per capita intake of fish in Brazil is 1.81 kg/year, a low consumption compared to Spain, which has a per capita infant consumption of fish of 3.26 kg/year **[24]**.

Data on fish consumption and, specifically, DHA in the Brazilian population are scarce. Especially regarding the population of pregnant and lactating women. Study by Forsyth et al. **[25]** indicates that DHA consumption in Brazil would be 104.3 mg/day, far from the recommendations. The same author points out that, in infants, the consumption of DHA of food in Brazil is between 30 and 60 mg, depending on whether or not it includes breast milk **[26]**. Study conducted by Wierzejska et al. **[27]** evaluated DHA intake in Polish pregnant women and observed a low intake of DHA (median: 60 mg/day). Another study that included Canadian women in the thirtieth week of gestation showed that 66.7% complied *with the Food and Agriculture Organization* (FAO)/World Health Organization (WHO) recommendation of 200 mg/d DHA, and only 48.1% complied with the Recommendation of the Canadian Academy of Nutrition and Dietetics of 500 mg/d DHA + EPA **[28]**.

Regarding the consumption of DHA by lactating women, Aumeistere et al. **[29]** evaluated DHA intake in breastfeeding women, as well as DHA levels in breast milk. The results showed that the mean maternal consumption of DHA was 150.3mg/day, lower than recommended (200 mg/day). The authors concluded that the consumption of marine fish is a significant positive predictor for DHA levels in breast milk. When it is not possible to evaluate the intake of DHA in a population, samples of biomarkers of adipose tissue can be used, as shown by Miles et al. **[30]** when evaluating the percentage of polyunsaturated FA in the samples of 840 individuals.

One strategy to increase the consumption of DHA food sources, is the nutritional and food orientation of the population, with tax incentives to decrease fish costs. When they are not the main preparation, they can be supporting in recipes such as broths, stews, roasts, pates, pancakes, sauces, salads, sandwiches, pies, fillings and various savories. According to the stage of life, from pregnancy, childhood to preschool age, considering the source foods, trends and lifestyle, specific preparations can be oriented for these different phases.

It is important to encourage the ingestion of cooking preparations with fish rich in DHA, for all ages and especially for pregnant women, since international guidelines have focused on their recommendations, much more on the harmful mercury content of fish than on the beneficial effects provided by their consumption. The orientation of fish consumption should be simple, objective and adequately disseminated, to achieve the impact, and may include visual content, use of technology and nutritional marketing **[31]**.

DHA and neurological development

For some decades now, it has been known that maternally breast-fed children have better cognitive performance than those fed in other ways. The reasons for this are many, starting with the mother-child bond. For example, nursing mothers are more likely to also stimulate their babies more. Focusing only on biological changes, the list of possible relevant factors is still extensive and, while recognizing this fact, here we will only address the role of DHA.

Cognition

The accumulation of DHA in the brain coincides with its period of accelerated growth, between the last trimester of pregnancy and the first two years of life. As there is no *new synthesis* of PUFA, this incorporation at the beginning of life depends on the transference from the mother or the formulas and elongation from ALA. The deposition of DHA in the brain is particularly pronounced at the end of pregnancy, considering the percentage of DHA over the total fatty acids incorporated, and much higher in the brain than in other tissues **[32]**. Dependence on maternal transfer can be evidenced by comparing breastfed babies, with an increase in cortical DHA, in contrast to infants fed with formulas without DHA and ARA, where this does not happen **[33]**.

Existing intervention studies have mainly used a combination of DHA and arachidonic acid (AA) instead of any of them alone, as this is how they occur in nature, and the importance of these LC-PUFAs has been widely demonstrated **[34]**. A review of year 2010 studies on n-3 LC-PUFA supplementation for pregnant or lactating mothers showed that supplemented babies had greater head circumference at two years, but there was no difference in ability to solve problems and psychomotor development **[35]**. In a more recent study, in animal model, the impact of supplementation of specific fatty acids of the brain on the development of the central nervous system was evaluated, observing volume cerebral total, total gray matter, callosum corpus and cortical volumes significantly higher when compared to the placebo group **[36]**. In addition, prenatal DHA has shown potential to positively modulate the attention of babies in the first year of age **[37]**, as well as at 5 years of age **[38]**, and DHA deficiency in the uterus increases the vulnerability of brain development **[39]**.

The interpretation of the effect of LC-PUFAs on cognition should be careful, since its unique definition is complex and the time to observe the effects is very wide. It is important to note that LCPUFA supplementation during pregnancy/childhood may have long-lasting effects on brain structure, function and neurochemical concentrations in regions associated with attention (parietal) and inhibition, as well as neurochemicals associated with neuronal integrity and brain cell signaling **[40]**. There are several problems in the comparison between studies in this area: the samples may be small, the DHA dose is variable, supplementation may be with pregnant, lactating or baby, and, not least, differences in the scales used to evaluate outcomes. Another important point is the level of DHA before the beginning of supplementation. As expected, more robust differences were observed in children of lower socioeconomic status and with indications of nutritional deficiencies **[41]**.

Malnutrition is not the only situation in which DHA supplementation may be relevant and may have an effect on other forms of insults to the brain in training. In this sense, supplementation with DHA in pregnant alcohol users could mitigate the deleterious effects of alcohol on the development of the baby **[42]**. And in this same sense vegan children with a mean age of 3.5 years had, among other alterations, markedly low concentrations of DHA **[43]**. The impact of this on cognitive development is yet to be determined. One conclusion could be that DHA supplementation has a better chance of effect in situations where there is a deficiency. However, deficiencies and sub-optimal intake are very common in most countries of the world, especially in Brazil **[26]**, whatever the reason may be. In this case, supplementation could be done not only in pregnancy and early childhood, but even in later stages, such as preschoolers.

Vision

In addition to the brain gray matter, large concentrations of DHA are found on the outside of the retinian rods, indicating their possible relevance to vision. This is an early relationship: the visual acuity of babies is associated with the concentration of DHA in breast milk, with lower concentrations (<0.17% of total fatty acids in milk) related to lower acuity **[44]**, and unfortunately, the concentration of DHA in breast milk has been decreasing over time in Western countries. Studies with full-term infants show conflicting results, probably due to methodological differences, but it is interesting to point out that in at least one study **[45]**, while for general cognition there was no difference between the supplemented and non-supplemented groups, the development of gestures and their total number was higher in the supplemented group. As the gestural abilities in children are associated with visual memory, we can interpret these results from the effect on vision development.

Studies with preterm babies are less numerous, but the results are more robust. Preterm infants have higher rates of learning and language difficulties, higher probability of attention deficit and hyperactivity and, as a group, worse cognitive performance than their full-term correspondents. The factors associated with a preterm birth are multiple and separating the weights of each variable is an arduous task, but, specifically on DHA, there is an obvious initial disadvantage: shorter pregnancy means that these babies have had less time to accumulate DHA, and to accumulate in the most critical period, which is the third trimester of pregnancy.

In at least one double blind study, supplementation for the lactating, or for the baby himself, when maternal breastfeeding was not possible, showed better visual development in the group supplemented as evaluated at 4 months by visual evoked potentials **[46]**, however, a study by the same group comparing the two groups of infants at 7 years of age showed no difference in relation to various visual processing measures, such as acuity, contrast sensitivity, stereopsis and visual perception **[47]**, and another study from a different group showed that infant formula DHA supplementation in 0.32% of total fatty acids improved visual acuity, while higher amounts of DHA supplementation were not associated with additional improvement **[48]**. It is natural to expect the effect to run out at some point; it may also be that the reduced ARA could be responsible for reducing the benefit on the cognitive outcomes seen at this dose **[49]**.

DHA supplementation in pregnancy and early life may have a beneficial effect on cognitive and visual development, but the results are conflicting for large-scale use. On the other hand, in specific groups, with a higher risk of low DHA concentration, the results are more convincing. It is recommended, for pregnant and lactating women, daily consumption of at least 200 mg of DHA or the equivalent of 2 to 3 servings of fish per week **[50]** or up to 1000 mg for the prevention of preterm delivery **[51,52]**. Infant formula should contain DHA between 0.2 and 0.5% of total fats **[53]** or a minimum of 20 mg DHA/100 kcal; and ARA:DHA ratio of at least 1:1 **[54]**.

DHA and inflammation

The immune system is responsible for protecting the host against the effects of infectious agents. The proper functioning of this system can be directly influenced by human nutrition. Regarding DHA supplementation, it is known that in certain conditions such as pregnancy, lactation or even in diseases such as cancer or sepsis, supplementation with ω-3 has shown positive effects on the immune system, as well as better prognosis due to its antiinflammatory properties **[55-57]**. And all suggest that intervention with ω-3 during pregnancy and/or lactation may influence the immune system of maturation of the fetus and baby and contain the development of allergic diseases **[57]**.

Considerable changes in the type of fat consumed in parallel to the increasing prevalence of atopic and allergic diseases were observed, such as atopic eczema, conjunctivitis, rhinitis and allergic asthma mediated by Immunoglobulin E (IgE), creating the hypothesis that this imbalance may have a causal relationship, since the proportions between fatty acids ω-6 and ω-3 have undergone significant changes. In some Western cultures, they went from a 1:1 balance (ω-6: ω-3) to almost 30:1 in some Western cultures **[58]**.

Diets rich in ω-6, due to increased consumption of linoleic acid (LA, 18:26) present in vegetable oils and arachidonic acid (AA, 20:4 ω-6) found in meats, contribute to the increase and predominance of pro-inflammatory arachidonic acid in tissues. This leads to consistent biochemical and physiological changes with a greater propensity to an inflammatory allergic response **[59]**. There are, therefore, plausible mechanisms in which diets rich in ω-3 fatty acids can modulate the development of IgE-mediated allergic diseases and regulate immune responses. Data from clinical and animal studies suggest that the provision of a nutrition with ω-3 at the beginning of life may favor the strengthening of the immune system and the function of immune cells by reducing inflammatory responses **[60]**.

The fetus receives EPA and DHA during pregnancy already from the 25th week of gestation, through the placenta, and also, after delivery, through breast milk **[61]**. Any event that affects these early responses can lead to unfavorable life-long consequences **[62]**. Omega 3 has been known for decades as a potent anti-inflammatory agent. The most common route by which lipids can modulate the biology of pro-inflammatory cytokines refers to the alteration of fatty acid composition in the cell membrane. This change directly influences the synthesis of eicosanoids and, thus, dietary supplementation with omega 3 exerts relevant effect and can modulate the biology of these inflammatory mediators derived from lipids, since it favors the synthesis of prostaglandins and series 3 and 5 leukotrienes that have reduced pro-inflammatory potential. It is also postulated that omega 3 fatty acids reduce the inflammatory process by inhibiting the signaling pathway of transcription factors such as NF-kB, in addition to other nuclear receptors related to inflammatory cascade **[63]**.

Scientific evidence also suggests DHA fatty acids may attenuate the pro-inflammatory state that is associated with obesity and metabolic syndrome **[64]**. In cross-sectional and cohort studies, the food intake of marine ω-3 was associated with lower plasma concentrations of inflammatory markers, including binding molecules and PCR **[65,66]**. Another intervention study showed that feeding containing marine ω-3 or fish oil or DHA supplementation showed results compatible with attenuation of inflammatory response in patients with DM2 and hypotriglyceridemic. Differences in population profile, form of administration, supplementation dose, parameters analyzed, and concomitant use of statins contribute to discrepant results. Therefore, the real clinical relevance of DHA supplementation for immunological and antiallergic effects is still not very well clarified **[13]**. However, especially within an appropriate dietary pattern, the reduction of the inflammatory process can be mediated by the intake of omega 3 fatty acid. Much is discussed about the ideal proportion between the intake of omega 6 and 3 fatty acids, it is usually recommended three parts of omega 6 for an omega 3 part (3:1), up to 5:1. From a 7:1 ratio, positive modulation of the inflammatory response may already occur **[63]**.

DHA and preconception period

A diet rich in macro and essential micronutrients is one of the fundamental pillars for a healthy life. In the reproductive aspect, differentiated feedings can, in fact, positively impact the couples fertility **[67]**, as well as promoting safer pregnancies, with a significant reduction in adverse outcomes, including prematurity **[68]** and hypertension **[69]**, in addition to protecting the health of the newborn, in short, medium and long terms **[70]**. The preconception period is a great opportunity for health promotion, improvements in maternal physiology, metabolism, body composition and nutritional status **[71,72]**. During this period, preventive interventions and plans are carried out on future pregnancy, including guidance on possible risks, food supplementation, educational and financial planning, among others **[73]**.

Among the various dietary modifications, the intake of omega-3 rich foods is one of the most important. In fact, the intake of omegas 3 at adequate levels is related to several positive effects for our health, such as reduction of risk of cardiovascular diseases **[74]**. Currently, there are also lines of research interested in the beneficial effects on male and female fertility **[75]**. According to the World Health Organization, infertility is a reproductive system disease defined by failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse **[76]**. Fertility problems have increasingly worried couples, since 15% of them are affected, and apparently, omega-3 seems to play a relevant role in this aspect.

It is estimated that, in the world, approximately 20 to 30% of women, including pregnant women, have some nutritional deficiency **[77]**, with increased risk for short-, medium- and long-term diseases **[15]**. It is not new that adequate dietary patterns, maintained throughout life, from birth, can avoid many health problems. According to the *Dietary Guidelines for Americans* (DGA, 2020–2025) **[78]**, an impaired diet provides higher risks of all-cause mortality, cardiovascular disease, cholesterol elevation, systemic arterial hypertension, obesity, type 2 diabetes, breast, colon and rectum cancer, hip fracture and bone diseases **[79]**. Currently, research lines investigating the effects of malnutrition on couples' fertility have also brought new knowledge about this important influence **[80]**.

Importance to the father

Omegas 3 are essential for good organic maintenance and have cardiovascular protective effects, as previously seen. However, the focus of this passage will be on the benefits of its intake regarding male fertility. It is estimated that 20 to 70% of couples' fertility problems are caused by some male factor **[81]**. Among the main causes of male infertility, we have reduced or poor sperm quality **[82]**. Three primary points are usually determined to evaluate sperm quality: sperm concentration, sperm morphology and sperm motility **[82]**.

Studies have shown a beneficial effect of omega-3 intake for men **[75]**. Adequate consumption is able to optimize the fatty acid composition of sperm and seminal plasma, increase libido, concentration and total sperm **[83]**, decrease morphological abnormalities **[84]** and increase the spermatic motility **[85]**. In a recent meta-analysis it was demonstrated that the supplementation of infertile men with omega-3 fatty acids resulted in a significant improvement in spermatic motility and DHA concentration in seminal plasma **[86]**. In another flagship study, Safarinejad and collaborators **[87]**, using EPA and DHA supplements for men with idiopathic oligospermia for 32 weeks, they observed a significant overall improvement, with an increase in sperm concentration from 15.6 ± 4.1 to 28.7 ± 4.4 × 106/ml (p=0.001), in motility from 18.7 ± to 2.4% to 27.4 ± 2.6% (p=0.002) and in strict normal morphology from 7.4 ± to 2.8% to 12.8 ± 2.6% (p=0.002).

It is believed that these benefits may be due to the influence of omegas 3 on steroid production pathways, such as increased testosterone concentration, the number of gonadotropin receptors involved in the regulation of steroidogenesis and also as a result of modification of the phospholipid profile of the sperm membrane facilitating an increase in fluidity and flexibility of the sperm membrane **[75]**.

Although the evidence on the benefits of an adequate intake of omega 3, or its supplementation for men, with the main purpose of optimizing the spermatic aspect and consequently improving the chances of a pregnancy in infertile couples due to male factor are increasing, the current literature still lacks further studies, with larger homogeneous cohorts, to evaluate their effect on spermograms, and thus demonstrate more robust evidence on supplements in the treatment of male factor infertility **[82]**.

Importance to the mother

With regard to improvements in aspects of female fertility, although there is no very clear evidence on the mechanisms of action, there seems to be better maturation and oocytorial development, reduction of anovulatory cycles and elevation in circulating progesterone levels, in addition to improvements in embryonic morphology **[88-92]**. Regarding infertility, in vitro fertilization (IVF) is recognized as one of the most effective treatments **[93]**. Although some factors associated with lower success of IVF treatment, such as advanced female age, are not modifiable, there is growing interest in the impact of possibly modifiable factors, such as diet, on treatment outcomes **[93]**.

Dietary factors are believed to be closely linked to the risk of developing reproductive disorders that may affect fertility, such as anovulatory cycles and endometriosis **[94-97]**. However, despite the possible relations with female fertility and fecundity, current studies of associations are widely ambiguous **[93]**. In the *Biocycle* study, increased omega 3 intake was associated with increased progesterone concentration, increased estrogen, and lower risk of anovulation **[91]**. In the PRESTO study **[98]**, omega 3 intake was also associated with higher fecundity, but no similar association was found in the *Snart Foraeldre cohort* **[97]**.

In relation to the potential effects on ovarian reserve, omega 3 administration decreased serum levels of follicle stimulating hormone (FSH) in women with normal weight, but not in obese women with normal ovarian reserve **[80]**, also showing results that are difficult to interpret. Given the current findings in the literature, there seems to be benefits of a balanced diet rich in omega 3 in female infertility, however, more evidence is needed to affirm this relationship with greater certainty. On the other hand, the benefit of omega 3 intake for reduction of outcomes during pregnancy and for long-term improvement to the conceptus **[68]**, justify the implementation of a healthier lifestyle, including the incorporation of an omega-3 diet from the early stages of reproductive planning.

Current recommendations suggest that the general population, including men and women of childbearing age, consume approximately 230 grams of seafood per week, equivalent to 2 to 3 servings of fish per week, providing approximately 250 mg of EPA and DHA per day **[79,99,100]**. Despite the recommendations, it is known that only a small portion of the population achieves this desirable intake of fish **[101,102]**. Added to this is a worrying dilemma concerning the toxicity of these fish in certain regions **[103]**. Thus, according to the region and cultural and local situations, each case should be individualized, evaluating the possibility of satisfactory omega 3 intake, or prescribing its supplementation.

DHA in the gestational period

It is well established that DHA is an important structural component of the human brain and retina **[104]**, representing about 80% of all polyunsaturated fatty acids of the retina, while 60% of the dry weight of the brain are fatty acids, of which DHA is the main omega-3 105. During fetal and infant development, the membranes of the retina and gray matter of the brain are abundantly enriched with DHA **[104]**. During the third trimester and up to two years of life, DHA selectively accumulates in the brain at a higher rate than other fatty acids **[105,106]**.

Since the last two decades, the benefits of omega-3 intake, especially DHA, during pregnancy and lactation are known. Studies have shown that increased DHA intake in pregnancy can improve maternal mood and neuronal development of the newborn, and there is a strong association between the dietary dose of DHA in pregnancy and the reduction of depressive symptoms in the postnatal period **[106]**. Other studies have linked the mother's DHA status at the end of pregnancy with improvements in neonatal sleep patterns **[107]**, attention deficit **[108]** and motor development **[109]**.

In its last systematic review, Cochrane **[68]** brought an important contribution on the importance of adequate omega-3 intake during pregnancy, whether in the form of feeding or supplementation, in the reduction of preterm delivery. In this meta-analysis, 70 CRTs were included, totaling 19,927 patients, comparing groups with increased omega-3 intake and groups without omega-3 or placebo. There was an 11% reduction in risk for childbirth below 37 weeks [RR 0.89, 95% CI (0.81 - 0.97); being 26 ECR, 10,304 patients], as well as a 42% reduction in the risk of delivery below 34 weeks [RR 0.58, 95% CI (0.44 - 0.77); being 9 CRT, 5204 patients], both with high quality of evidence, the number necessary for treatment being of 68 and 52, respectively. In this review, an increased risk for deliveries above 42 weeks was also reported in the groups that used more omega-3 [RR 1.61, 95% CI (1.11 - 2.33); 6 CRT, 5141 patients]. No differences were found in relation to maternal death (RR 1.69, 95 CI, 0.07 - 39.30), preeclampsia (RR 0.84, 95% CI, 0.69 - 1.01), eclampsia (RR 0.14, CI 95%, 0.01 - 2.70), abortion (RR 1.07, 95% CI, 0.80 - 1.43), gestational diabetes (RR 1.02, 95% CI, 0.83 - 1.26), perinatal death (RR 0.75, 95% CI, 0.54 – 1.03), fetal growth restriction or small for gestational age (RR 1.01, 95% CI, 0.90 - 1.13) and fetal death (RR 0.94, 95% CI, 0.62 - 1.42) **[68]**.

The maternal diet is of great importance because it determines the type of fatty acid that will accumulate in fetal tissue. The transport of essential fatty acids is carried out through the placenta and deposited in the brain and retina of the conceptus, and this deposit occurs mainly in the last trimester of pregnancy. In this quarter, the fetus removes a total of 50 to 75 mg of LCPUFA from the mother, most of which are DHA **[110-114]**. Maternal consumption of DHA (in the form of fish and/or supplementation with fish oil), essential for the formation of all cell membranes of the central nervous system, can prolong high-risk pregnancies, increase newborn weight, length and circumference of the head at birth and increase visual acuity, hand-eye coordination, attention, problem solving and information processing **[115]**. Improvement of immunity and response of the autonomic nervous system is also involved **[110-114]**. ImhoffKunsch andt al. found, in a randomized, double-blind clinical study, that maternal intake of 400 mg of DHA decreased the occurrence of upper airway infections in the first month of life and the number of disease days at 1, 3 and 6 months of age **[112]**. In the placebo-controlled study, by Gustafson et al., it has been shown that supplementation of 600 mg of DHA resulted in a more responsive autonomic nervous system of the fetus and newborn, giving them adaptive advantage. This study showed the effect of maternal supplementation with DHA on the metabolic programming of the fetus **[116]**.

In pregnancy, however, there are situations that can alter the intake of these acids, such as: inadequate nutrition, consumption of fat and oils with high proportion of omega-6 and very low omega-3 intake (which is very common) and frequent and multiple pregnancies **[117]**. However, lower DHA intake has been observed, perhaps because it is so widespread that fats should not be ingested in general or because of insufficient fish intake, and especially if the mother is a vegetarian **[113,114,118,119]**. Torres & Trugo reviewed the intake of LCPUFA sources, as well as the serum level of DHA in Brazilian pregnant women, and found lower intake and lower serum level, compared with international data **[120]**. Numerous studies have shown that maternal intake of DHA in pregnancy increases blood deposits **[110,111,113,114,121]**.

Whether DHA can be obtained by ingestion of marine fish or by supplementation with fresh fish oil is much discussed in the literature. The amount of DHA among marine fish species varies greatly: for every 100 g there is 0.12 g in fried hake fillet, 0.45 g in fried white hake, 0.36 g in fried sardines, 0.46 g in canned sardines in oil, 0.05 g in roasted corvina and 0.05 g in shark. It may be suggested that the intake of 300 g per week of white hake or sardines in oil is sufficient. For other types of fish, the amount ingested would need to be much higher, which could bring risk of mercury poisoning **[122]**. In this sense, the intake of predatory fish (shark, tuna) should be a maximum of 150 g per week **[120]**. According to Bonhamand et al., who evaluated whether there was an association between the amount of fish ingested by pregnant women and DHA levels, even with an average intake of 526 g fish/week, they verified that serum DHA levels remained low, especially in the last trimester **[123]**. Noakes et al. also found that, in the group of pregnant women with salmon intake twice a week, compared with the group with low fish intake, no control was verified in the appearance of atopy markers in the child at 6 months of age **[124]**. These findings were similar to those of Garcia-Rodriguez et al., who found no change in cytokine levels and inflammatory biomarkers in pregnant women who ingested 150 g of salmon per week **[125]**. These data point to the difficulty in making recommendations based on fish consumption. Additionally, the consumption of fish oil capsules can lead to the same problems, and the concentration of DHA and the degree of safety (relative to mercury) are uncertain **[126-128]**. Thus, supplementation, when indicated, has preferably been done with DHA produced from the cultivation of algae, such as *Schizochytrium sp* **[129]**.

The recommended doses of DHA supplementation, as well as its sources, are very variable among studies. 500 mg DHA + 150 mg eicosapentaenoic acid (EPA) has already been suggested; 600 mg DHA + 140 mg EPA; 4 g fish oil (2.24 g DHA + 1.12 g EPA); 1.1 g DHA + 1.6 g EPA; 800 mg DHA + 100 mg EPA; 1183 mg DHA; 400 mg DHA; 100 mg, 400 mg, 600 mg, 800 mg, 900 mg, 2.0 g and 2.2 g DHA **[110-114,116,120,123-125]**. Side effects secondary to supplementation may occur, such as bleeding (due to inhibition of placental aggregation), immune response depression and gastrointestinal intolerance **[119]**. Carlson et al. compared 600 mg DHA supplementation with placebo in 350 pregnant women less than 20 weeks of gestation in a randomized, double-blind cohort study conducted from January 2006 to October 2011. In both groups, the intake was 77% of the capsules, which meant that 469 mg of DHA was ingested in the treated group. They verified that, in the group supplemented with DHA, the duration of pregnancy was longer, as well as the weight and length of the newborn, in addition to the fact that this supplementation was safe **[111]**.

The fetus is totally dependent on maternal nutrition for growth and development, that being an extremely important aspect. Thus, if the mother receives a diet with an adequate supply of unsaturated fatty acids, it can offer the fetus the necessary amount of these acids for a good development of the nervous and visual system, gestation time, nutritional aspects of the newborn, immunity, among others. And it appears that fish intake may not increase maternal DHA for these beneficial effects to occur **[110,113,114,119]**. Therefore, the set of evidence indicates the supplementation of DHA for all pregnant women, especially in the last two trimesters of gestation, and the doses vary, even considering only the best quality studies, between 200 and 600 mg per day **[111]**, preferably with safe source DHA.

Ren et al **[130]** in a systematic review study with meta-analysis support a relationship between maternal or neonatal n-3 fatty acid levels and birth weight of offspring and weight development in childhood. This was specifically the case for high doses of DHA and/or EPA supplementation > 650 mg/day, while no association was found between low doses of supplementation and weight development. According to Jonathan G. Mun **[131]** and West **[132]** phosphatidylcholine-DHA levels are higher in pregnant women than in non-pregnant women, suggesting a higher demand for methyl donors and increased PEMT activity. In addition, they showed that when choline and DHA were supplemented in non-pregnant women, higher choline intake resulted in higher PC-DHA enrichment, suggesting that higher choline intake may increase PEMT activity. These findings suggest a metabolic synergy between choline and DHA.

Tressou et al **[133]** in the national research INCA2 pointed out that the majority of the French population (children, adolescents, adults and the elderly) ingests low amounts of polyunsaturated fatty acid n-3 (PUFA) both in the form of precursor (alpha-linolenic acid, ALA) and long-chain acid (mainly docosahexaenoic acid, DHA, including pregnant and lactating). Carlson et al **[134]** report that there is "limited evidence" for a favorable effect of supplementation in pregnancy on cognitive outcomes and "insufficient evidence" to evaluate other developmental outcomes. According to Philippa Middleton **[68]** preterm delivery (< 37 weeks) and early premature delivery (< 34 weeks) were reduced in women who received omega-3 long-chain PUFA compared to no omega-3.

Effects of impaired nutritional status on the mother

Deng et al. **[135]** suggest that the intake of DHA (>185 mg/day) results in increased concentrations of DHA in breast milk. This finding suggests that mothers with inadequate DHA intake should change their eating habits to consume a DHA-rich diet or take enough DHA supplements to meet the average nutritional needs of babies. According to Diana C. CastroRodríguez **[136]** pregnancy and lactation should be seen as a window of opportunity for the development and establishment of interventions that have beneficial effects on maternal metabolism, which brings possibilities for prevention of adverse metabolic programming of offspring.

Effects of impaired nutritional status on the fetus

Srugo et al **[137]** studied the effect of malnutrition during pregnancy in mice and showed the impact on Paneth cell function of the fetal intestine and on the development of vital cells for intestinal barrier function and gut-brain axis connection. The results indicate that malnutrition before and during pregnancy has adverse consequences for fetal bowel development, maternal and fetal intestinal function, and potentially long-term programming of intestinal and cerebral function and intestinal immunity. According to Setyaningrum Rahmawaty **[138]** consumption of DHA during pregnancy results in increased cognition in offspring. Foos enriched with specific nutrients, such as ω-3, can lead to relatively rapid changes in the specific nutritional status of a community, and is a cost-effective public health intervention.

Effects of impaired nutritional status on childbirth

According to Zhu et al. **[139]** maternal plasma phospholipid PUFAs are implicated in fetal growth and their roles may vary according to pre-gestational obesity and the time of pregnancy.

Intake and supplementation during pregnancy and lactation

Zhang et al. **[102]** report that most pregnant and child-age women in the U.S. consume significantly lower amounts of seafood than recommended by the DGA, which subsequently leads to a low intake of EPA and DHA. According to Braarud et al **[140]** the results emphasize the importance of pregnant and lactating women having a satisfactory status of DHA from the food intake of marine fish or other DHA rich sources. Wierzejska et al **[27]** found that the diet of pregnant women is quite deficient with regard to the intake of DHA. It is important to emphasize that it is not possible to comply with current recommendations without dietary supplementation. According to Jackson et al. **[141]** it is not known whether the standard recommendation of at least 200 mg/day of supplemental DHA during lactation is sufficient for most women to achieve a desirable level of erythrocytes and DHA in breast milk.

Lehner et al. **[142]** report that the reasons for inconclusive results on the supplementation of pregnant and lactating women may be small samples for each category evaluated, questionable quality of the included studies and the difficulty of reliably measuring cognitive performance in young children. Blood levels of n-3 LC-PUFAs are not mostly comparable. Moreover, the influence of genetic and environmental factors could not be evaluated. Future studies in this field should address such deficiencies. According to Nevins et al. **[143]**, limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child and, according to Carlson et al. **[111]** a 600 mg DHA per day supplement in the last half of pregnancy resulted in longer overall gestations durations and increased baby size. A reduction in preterm infants and very low birth weight may be important clinical and public health outcomes od DHA supplementation.

Given the large body of evidence available in favor of the use of omega-3 in pregnancy and lactation, the medical professional should be attentive to evaluate the actual intake of omega-3 of their patients, alerting to ingestion of 2 to 3 parts of fish per week. Should be careful to advise on possible fish not enriched with omega 3, as well as the risk of ingestion of deep water fish or places where there may be an increased risk of heavy metal contamination. In situations where it is not possible to perform sufficient DHA intake, assistant professionals should make use of DHA supplementation.

DHA in childhood and adolescence

The n-6 and n-3 series of long-chain polyunsaturated fatty acids (LCPUFA) play an important role during pregnancy, lactation and childhood, since they are constituents of phospholipids of the cell membrane and precursors of eicosanoids, besides being considered essential for the maturation of the developing brain, retina and other organs **[144]**. Docosahexaenoic acid (DHA) and arachidonic acid (ARA) are biosynthesized from essential fatty acids, alpha-linolenic and linoleic, respectively, by successive stages of desaturation and stretching in the intestine, liver and brain **[145]**.

Omega 3 polyunsaturated fatty acids such as DHA and eicosapentaenoic acid (EPA) are considered conditionally essential, with critical roles during the initial development of the retina and brain, and have other benefits, such as anti-inflammatory effects. In addition, EPA and DHA are direct precursors of specialized pro-resolution mediators, a new class of lipid mediators, including three main families: resolvines, protectines, and maresins. In animal disease models, it has been shown that these mediators control the duration and magnitude of inflammation and may accelerate the return to tissue homeostasis after infection **[144]**.

Infant and preschool

The first years of life are very important, as they constitute a unique window of opportunity to modulate various organs and systems of the fetus/newborn/infant from a functional and metabolic point of view, shaping future health **[145]**. The rapid growth in the first two years of life is also accompanied by increased organs and tissues. The brain has its growth extremely accelerated in fetal life and in the first years of life. There is a strong correlation between adequate nutrition and cognitive and visual development in children **[146]**. LCPUFA (EPA, DHA and ARA) have great performance in this period, being crucial for growth, cognitive performance, vision and immune system. Lipids are of critical importance in this growing period because they are the macronutrients with the highest caloric density. In addition, DHA along with arachidonic acid are the main lipid components of brain tissues and are fundamental for the brain and visual development of the child 146. DHA is preferably incorporated into the brain and retinas composition in the last trimester of pregnancy and in the first two years of life **[147]**.

DHA is considered essential for normal brain function, being the main fatty acid present in the gray matter of the brain. Corresponds to 15% of the total composition of fatty acids in the human frontal cortex and affects the pathways of neurotransmitters, synaptic transmission and transduction of signals **[147]**. The deficiency of this acid can alter the composition of the synaptic membranes, affecting the functions of neuronal membrane receptors, ionic and enzymatic channels **[148]**.

In addition, DHA is at high concentrations in the membranes of the cones and rods of the retina, giving them the ideal fluidity for the process of transduction of the luminous signal in electrical signal processed by the brain **[149]**. There is strong evidence for a causal relation between lipid phospholipids containing brain DHA and visual and neurological development. Many studies have shown that higher plasma concentrations of DHA obtained at the expense of dietary supplementation correlate positively with infantile neurocognitive and visual development **[149]**. In meta-analysis, published by Qawasmi et al, significant benefit has been demonstrated in supplementing infant formulas with long chain polyunsaturated fatty acids in the visual acuity of children at various stages of development in the first year of life **[150]**.

The fetus, because it does not have full capacity to synthesize long-chain polyunsaturated fatty acids from its precursors ω-3 and ω-6, has its necessity supplied by the placenta. Therefore, in the last trimester of pregnancy, this organ establishes preference in the transport of docosahexaenoic and arachidonic acids **[146]**. After birth, the needs of these two polyunsaturated fatty acids remain exacerbated due to bodily needs. In addition, the hepatic immaturity of the newborn hinders their production, through their precursors, the essential fatty acids linoleic and alpha linolenic. Therefore, the supply of DHA by diet, especially breast milk, is indispensable **[151]**. However, the concentrations of docosahexaenoic acid in human milk depend on the maternal diet, which is not always rich in ω-3 **[152]**.

It is important to emphasize that, in the introduction of complementary foods, it is important to verify that children are receiving EPA, DHA and ARA at effective levels. **Tables 2** and **3** summarize some of the information presented above.

According to the World Health Organization, the ideal food for the infant is breast milk, offered on free demand, exclusively up to the sixth month of life and in

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conjunction with complementary feeding up to two years or more. Human milk has a balanced nutritional composition, which includes all essential nutrients, in addition to a large number of conditionally essential and approximately 45 different types of bioactive factors **[154]**.

Table 2. DHA deficiency and impairment of cognitive and visual development in children.

Impairment of cognitive development	*Smaller number of nerve cells* *Less DHA in nerve cells* *Lower production of neurotransmitters (acetylcholine, dopamine and norepinephrine)* *Lower myelin deposition* *Fewer synapses*
Impairment in visual development	Inadequate functional maturation of the retina Less differentiation of photoreceptors

Adapted from: Lauritzen et al (2016) **[144]**.

Table 3. Mechanisms of action of DHA in immune and inflammatory cells.

Effect	*Mechanisms involved*
↓ production of eicosanoids derived from arachidonic acid	↓ arachidonic acid in membrane phospholipid Inhibition of arachidonic acid production Inhibition of arachidonic acid metabolism ↓ expression of the cycloxygenase-2 gene
↑ EPA eicosanoids production	↑ EPA in membrane phospholipid
↑ synthesis of resolvines and protectines	↑ DHA in membrane phospholipid Inhibition of arachidonic acid metabolism
↓ production of inflammatory cytokines	↓ expression of inflammatory cytokines (lower activation of nuclear factor kappa beta)
↓ chemotaxis of leukocytes	↓ chemotactic production ↓ expression of chemotactic receptors
↓ T-cell reactivity	↓ generation of intracellular signals due to cell membrane rupture
↓ presentation of antigens	↓ expression of class I major histocompatibility due to cell membrane rupture

Adapted from Calder PC (2013) **[153]**.

It is already established that DHA is present in the lipid profile of human milk, in concentrations ranging from 0.2% to 0.4% of total lipids. However, the presence of this fatty acid in breast milk depends on two physiological situations: 1st: maternal ingestion of the precursor (alpha-linolenic acid) and enzymatic conversion for lengthening and desaturation until the final synthesis of DHA or 2nd: maternal DHA supplementation. Thus, the first situation is dependent on the presence of enzymes in the metabolism of the omega 3 chain, a fact that is currently impossible to measure **[145]**.

Corroborating this fact, two Brazilian publications (2009 and 2013) **[155,156]** showed extremely low amounts of DHA in the milk of healthy mothers, reinforcing the need for the second situation described above, i.e., lactating supplementation with at least 200 mg of DHA, as already described in the I Consensus of the Brazilian Nutrology Association on DHA recommendations during pregnancy, lactation and childhood (2014) **[6]**. In the absence or impossibility of breastfeeding, the use of infant formulas is indicated, therefore, special attention should be given to the amounts of DHA present in these compounds, emphasizing that not all formulas available on the market are increased with this long-chain polyunsaturated fatty acid **[145]**.

Minimum requirements or recommended dietary intake (DRI) of DHA are still unknown in childhood **[151,157,158]**. In infants, there are strong theoretical arguments in favor of DHA supplementation, fundamentally with the idea of imitating breast milk, although the results of intervention studies in relation to cognitive and visual performance are controversial, as they are different in methodology, doses, responses and follow-up time **[8,159-161]**. The studies of Birch and collaborators contributed to highlight the need of DHA for the development of child visual acuity. In these studies, infants were fed a diet with different levels of DHA and, at the end of 52 weeks, those fed a supplemented formula presented visual acuity, assessed by evoked potential, significantly higher **[48,162]**.

Originally, infant formulas were not supplemented with DHA and ARA, contained only precursors (alpha-linolenic and linoleic), so infants should synthesize their own DHA and ARA. Subsequently, due to the recommendations of international organizations, such as ESPGHAN, these fatty acids were added to infant formulae with advantages for the overall development of the infant **[163]**. Adapting to the gold standard (human milk), infant formulas should contain amounts of DHA similar to breast milk (0.2% to 0.5% of the total amount of lipids) **[164]**.

The nutritional demand of the infant up to six months of life is exclusively milky. From this period, it becomes necessary to introduce complementary feeding, aiming at the adequate supply of energy, proteins, vitamins and minerals. The adequacy of nutrients in the complementary feeding is one of the factors that act in the prevention of morbidity in childhood, including overweight and malnutrition. To this end, this diet should contain adequate amounts of DHA (10-12mg/kg/day between 6 and 24 months of age), with the supply of food source of this nutrient, such as marine fish, mainly cold and deep waters (salmon, tuna, mackerel, cod, sardines, etc.) which contains larger amounts of this omega 3 fatty acid **[6]**.

In the preschool phase, i.e., between 2 and 6 years of age, DHA recommendations range from 100 to 200 mg/day. Thus, food source of this nutrient continue to be recommended to reach the daily amounts **[165]**. Table 4 provides information on recommendations for different pediatric age groups. Ideally, the daily supply of DHA should be achieved by diet. However, in several situations this is not possible, and it is important to use supplementation of this nutrient. Supplements for the pediatric range contain DHA extracted, basically from two sources: algae oil or marine fish. DHA extracted from green microalgae *Schizochytrium sp*, is a 100% vegetable product, free of heavy metals and contaminants, because these algae are grown in a controlled environment (marine farms). Because it derives from algae is an alternative for vegetarians, vegans, allergic to fish and pregnant women, and, in these cases, the origin of the capsules used as vehicle should be checked, which may contain collagen.

Currently, DHA derived from fish oil has a higher degree of purity, as heavy metals and contaminant products have been extracted and are elaborated with techniques that do not degrade or desaturate fatty acids. These supplements can be found in the liquid form to be offered in drops for younger children, and in the form of capsules, for later ages.

Table 4. Daily recommendation of DHA in lactating women, infants and preschoolers.

Population		*Amount of DHA*
Lactating		Minimum of 200 mg/day
Children	0 to 6 months	0.2 to 0.4% of total lipids
	6 to 24 months	10 to 12 mg/kg/day
	2 to 4 years	100 to 150 mg/day
	4 to 6 years	150 to 200 mg/day

Adapted from: FAO/WHO **[165]** e Nogueira-de-Almeida CA et al. **[6]**.

In conclusion, newborns and infants should receive sufficient amounts of long-chain polyunsaturated fatty acids to promote optimal visual and cognitive development, since the needs and importance of these acids in infant nutrition are established. Breastfeeding, as long as the mother ingests a sufficient amount of DHA, addresses the needs of these infants. In the absence of breast milk, infant formulas enriched with DHA (0.2% to 0.5% of total lipids) should be used. After six months of age, supplementation with this acid should be continued, although there are questions about the ideal amount to achieve the benefits provided by this nutrient.

Schoolchildren and adolescents

Frontal lobes have a high concentration of long-chain fatty acids (LCFA), particulary DHA, which is also essential for the development of these regions. In fact, DHA contributes 15% of total fatty acids in the human frontal cortex **[166]**. DHA is relevant for neurotransmission systems and for maintaining the synaptic viability. Experimental and clinical studies show that, additionally, DHA is important for glucose uptake and metabolism and some of its bioactive metabolites protect tissues from oxidative stress **[167]**. In this sense, and considering the role of the frontal lobes, it is not surprising that low levels of brain concentration of DHA in laboratory animals leads to changes in memory, learning and behavior **[168]**. High levels of LCPUFAs are also present in the nuclei of the base, pre- and post-central cortex, hippocampus and thalamus in newborn baboons, reinforcing their role in memory and suggesting importance in the integration between sensory and motor information **[169]**. In humans, DHA is important for two areas: the brain and retina. It also plays a role in other areas, such as bone development.

The effect of adequate amounts of DHA on pregnancy, breastfeeding and early childhood remains long-term. Prospective investigation from birth with Inuit children (mean age: 11 years), an Arctic ethnic group whose diet is basically based on fish and other marine products, showed a correlation between DHA concentration in umbilical cord blood and neurophysiological measures (event-related potential for visual recognition), with lower response latency time and amplitude of the late-term positive component greater. They also performed better in memory tests **[170]**. Assuming pregnancy and breastfeeding with inadequate diets in relation to DHA, it is possible to think whether supplementation, for example, with fishmeal, for school-age children, could make a difference. The results are unclear: one study did not confirm preliminary results of improvement in memory capacity and verbal learning, in children between 6 and 10 years of age, with supplementation **[171]**, results similar to those of other investigations **[172]**. Supplementation in healthy children aged between 10 and 12 years using computerized tests showed no significant differences in an 8-week intervention **[173]**. On the other hand, more accurate measurements, using functional magnetic resonance imaging to evaluate cortical activity during a sustained attention test, showed greater cortical activation in the dorsolateral prefrontal region in the group with supplementation, but both groups showed ceiling effect on the test, not differing performance **[174]**.

The results may be different in children with learning difficulties and probability of insufficient concentrations of DHA. Children at the beginning of school life with reading difficulties improve with supplementation **[175]** and the ability to spell remained among children with supplementation, while worsening in the placebo group **[175]**. These results are not necessarily in contradiction with previous studies, which have not shown differences in specific tests, but may indicate that subtle changes in different areas of cognition can have a synergistic effect and make a relevant difference in learning.

Dietary supplementation with long-chain fatty acids (LCPUFA), including docosahexaenoic acid (DHA), has been widely studied and discussed in recent years, but especially in pregnancy and early childhood. The main focus for supplementation has been on neurocognitive benefits and, more recently, on anti-inflammatory properties. Currently, DHA supplementation in schoolchildren and adolescent scans has been considered, based on the antiinflammatory effect on metabolic syndrome management, adjuvant cancer treatment, and its effect on the central nervous system, improving memory, reading and behavior, and symptoms of attention deficit hyperactivity disorder.

Regarding the use of DHA in the management of children and adolescents with attention deficit hyperactivity disorder, some authors argue that there would be a promising use in individuals still very young for medication use or using multiple drugs **[176-179]**. However, most still consider this prescription early, as recent randomized controlled trials do not show efficacy **[180-182]**. Perhaps, a more indicated use in those with dry and scaly skin, eczema and dry eyes, which may indicate deficiency of essential fatty acids such as LC PUFA **[183]**. Montgomery P et al **[184]** evaluated the efficacy of DHA supplementation in learning and behavior in healthy schoolchildren. In this randomized, double-blind, placebo-controlled study, they evaluated 376 children aged 7 to 9 years with poor reading performance and supplemented with 600mg/day DHA for 16 weeks. They did not find consistent differences between intervention and placebo groups in relation to reading, memory and behavior change. LópezAlarcón et al **[185]** studied whether LCPUFA-DHA supplementation would reduce insulin resistance and weight of obese adolescents. In a double-blind trial, 366 obese adolescents randomly received 1.2 g of DHA or 1 g of sunflower oil daily for 3 months. In this study, no anti-inflammatory effect of DHA was verified, decreasing metabolic syndrome. It is noteworthy that there was loss of many individuals and perhaps the time of use was small. DHA supplementation has also been considered in the management of nonalcoholic fatty liver disease. Recent clinical trials and meta-analyses evaluating LCPUFA-DHA supplementation appear to be effective and safe, but there is still no consensus on the dose and further studies, especially longitudinal studies, are needed **[186]**. With these data, we can conclude that the use of DHA in behavioral diseases and cognition and based on its anti-inflammatory effect is promising, although it cannot yet be recommended for children and adolescents unanimously.

In addition to the discussion about the indications for the use of DHA in schoolchildren and adolescents, it is also widely studied which dose should be prescribed. Ljungblad L et al **[187]** tried to establish a dose of LCPUFA in the complementation of cancer treatment. They evaluated 33 children in cancer remission and were able to show that a dose of 1500mg/body surface area of eicosapentaenoic acid (EPA) and DHA in the 40:60 proportion for 90 days was safe and reached adequate serum levels. Wurf et al **[188]** performed a review to identify the appropriate level of omega-3 index (IO3), the minimum daily dose of DHA to improve cognition in people 4 to 25 years of age. Analyzing 33 studies, they concluded that a positive effect on cognition was more likely when there was an increase from >6%; and when the daily supplementation dose is greater than or equal to 450 mg of DHA (in the various studies, the prescribed dose of DHA ranged from 16.2 to 1200mg/day).

Therefore, when prescribed, at the present time the DHA dose should be higher and equal to 450 mg and it appears that high doses such as 1200mg/day would still be safe. It is believed that there is already consensus that we should ensure that children and adolescents are ingesting the recommended doses of LCPUFA for age and sex, because their function in the body is very important. To this do, Herter-Aeberli I et al **[189]** developed the Swiss n-3 PUFA FFQ - a validated food frequency questionnaire for the intake of DHA and EPA, so that population groups at risk of low intake can be determined.

Final conclusions and recommendations

WHEREAS:

1) The first years of life are very important, as they constitute a unique window of opportunities to modulate various organs and systems of the fetus/newborn/infant from the functional and metabolic point of view, shaping future health, and the LCPUFA (EPA, DHA and ARA) has great performance at that time, being crucial for growth, cognitive performance, vision and immune system;

2) DHA is fundamental for child development, especially with regard to vision and the central nervous system;

3) Consumption of DHA during pregnancy results in increased cognition in offspring;

4) DHA supplementation in pregnancy and early life may have a beneficial effect on the cognitive and visual development of the fetus and infant, but the results are conflicting for large-scale use. On the other hand, in specific groups, with a higher risk of low DHA concentration, the results are more convincing.

5) The concentration of DHA in breast milk is dependent on the maternal nutritional status of DHA;

6) A systematic review study with meta-analysis supports a relationship between maternal or neonatal n-3 fatty acid levels and birth weight of offspring and weight development in childhood;

7) intake of DHA results in increased concentrations of DHA in breast milk;

8) Currently, DHA supplementation in school and adolescent has been considered, based on the anti-inflammatory effect on the management of metabolic syndrome, the adjuvant treatment of cancer, and its effect on the central nervous system, improving memory, reading and behavior, and symptoms of attention deficit hyperactivity disorder;

9) In adults, increased DHA consumption may slightly reduce the risk of coronary death and coronary events in adults, and consumption of EPA and DHA reduces triacyclglycerols levels;

10) The actual clinical relevance of DHA supplementation to immunological and antiallergic effects is not yet very well understood, but scientific evidence suggests that DHA may attenuate the pro-inflammatory state that is associated with obesity and metabolic syndrome and within an appropriate dietary pattern, the reduction of the inflammatory process may be mediated by omega 3 fatty acid intake;

11) Studies have shown beneficial effect of omega 3 intake for men and adequate consumption is able to optimize the fatty acid composition of sperm and seminal plasma, increase libido, concentration and total number of spermatozoa, decrease morphological abnormalities and increase sperm motility;

12) There seem to be benefits of a balanced and omega-3-rich diet in female infertility, however, more evidence is needed to affirm this relationship with greater certainty. On the other hand, the benefit of omega 3 intake to reduce outcomes during pregnancy and for long-term improvement to the conceptus, justify the incorporation of an omega-3 diet from the early stages of reproductive planning;

13) Supplementation with DHA has a greater chance of effect in situations where there is a deficiency, whatever the reason. In this case supplementation should be done not only in pregnancy and early childhood, but even in later stages, such as preschoolers;

14) Although alpha-linolenic acid plays a substrate role in DHA synthesis, it is not known for sure which percentage is actually converted, but it is estimated to be quite low, around 0.5% and adequate levels of DHA are not reached by pregnant women, lactating women and children;

15) DHA food sources are found mainly in marine fish and algae and its consumption in Brazil is low among children and among adults;

16) Raising fish consumption can lead to the ingestion of contaminants often present in this source, especially heavy metals;

17) A non-measurable part of the fish consumed in Brazil is raised in captivity and there is no regulation, with regard to DHA, in relation to the composition of the rations used;

18) There is high demand for fish oil-based supplements, which leads many industries to be willing to manufacture them. When the company does not have adequate raw material control, these supplements may have varying concentrations of DHA and may present contamination by heavy metals, especially mercury, reflecting the profile of the animal sources from which they were obtained.

IT IS RECOMMENDED THAT:

1) The healthcare professional should carefully investigate the intake of DHA, not only observing the daily amounts, but also food safety relative to its sources, in order to prevent the ingestion of heavy metals, especially mercury;

2) Supplementation with 2 to 4 g/day of EPA and DHA to reduce plasma triglyceride concentration by between 25% and 30% in individuals with severe hypertriglyceridemia (> 500 mg/dL) as part of treatment;

3) For men and women of childbearing age, as well as pregnant women, lactating women, children and adolescents, all conditions should be ensured so that the nutritional status of DHA is adequate, which can be obtained through diet or supplementation;

4) When choosing to use marine fish such as tuna, salmon and herring, this should be done cautiously, avoiding consumption if the food is not safe due to the risks of heavy metal contamination. It is also important to know the origin of the heavy, since many captivebred fish are fed non-DHA-fortified feed, which means that these fish should not be considered as suitable sources. One serving of fish is approximately 120 grams, so the recommended intake is 3 servings/week (360 grams/week). If in doubt, it is suggested to ensure intake through DHA supplementation;

5) It is recommended for pregnant and lactating women daily intake of at least 200 mg of DHA. Due to the low consumption of fish in Brazil and the insufficient conversion in ALA into DHA, and considering the high relevance of DHA for child development, regardless of diet, all pregnant women should receive daily DHA supplementation at a dose of 200 mg, preferably obtained industrially through algae;

6) Breastfeeding should be stimulated until two years of age, since, ensuring the adequate nutritional status of lactating DHA, breast milk will meet the infant's DHA needs;

7) Since the World Health Organization recommends maintaining breastfeeding until 24 months of age, and breast milk being the source of DHA, children aged 6 to 24 months should receive DHA through their dairy source, which should contain DHA content equivalent to 0.2% to 0.5% of total lipids;

8) Children over the age of 24 months, especially during the first five years of life, should have guaranteed adequate and sufficient dietary intake of omega-3 lipids in order to have adequate endogenous DHA production, as well as should be encouraged to consume direct nutritional sources of DHA. In case of proven dietary deficiency, supplementation with sufficient quantity should be considered for recommendations (100 to 150 mg/day between 2 and 4 years and 150 to

200mg/day between 4 and 6 years) to be achieved.

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Informed consent

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No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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