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Omega-3/omega-6 fatty acids: Effects on growth and neurodevelopment of the fetus and preterm infant. A narrative review.

Ácidos grasos omega-3/omega-6: efectos en el crecimiento y neurodesarrollo del feto y del recién recién nacido prematuro. Una revisión narrativa

Giulio Perrotta

Abstract

BACKGROUND: Fatty acids of the omega-3/omega-6 groups are used in cases of pregnancy, lactation and preterm birth. In recent decades, pediatrics has been trying to find out whether the use of omega-3/omega-6 has effects on human growth and neurodevelopment.

MATERIALS AND METHODS: A total of 44 original articles on the topic of omega-3/omega-6 and human growth and nutrition, in gynecology and pediatrics have been selected on PubMed from January 1979 until March 2023.

RESULTS: Significant critical issues emerged regarding published studies, despite encouraging evidence on the usefulness of omega-3/omega-6 used in pregnancy, lactation, states of malnutrition, and inflammatory processes, while data on the efficacy of use in fetal, neonatal, and pediatric patients are conflicting. Critical structural and functional issues emerge in the studies that may call into question the validity of the results.

CONCLUSIONS: The data are encouraging and suggest that certain aspects of the type of administration and dosages of omega-3/omega-6 fatty acid supplementation should be investigated further to help demonstrate the clinical validity of such prescriptions, especially in terms of gestational maturation, growth, and human nutrition in clinical practice in Gynecology and Pediatrics.

KEYWORDS: Docosahexaenoic acid; Thymnodonic or eicosapentaenoic acid; Omega-3; Omega-6; Fetus; Preterm; Infant; Dietary supplement.

Resumen

ANTECEDENTES: Los ácidos grasos omega-3/omega-6 se prescriben durante el embarazo, la lactancia y en paciente con parto prematuro. En las últimas décadas se ha intentado averiguar si la indicación de omega-3/omega-6 tiene efectos en el crecimiento y el neurodesarrollo en humanos.

Department of Clinical and Specialty Sciences (DISCO), Marche Polytechnic University, Salesi Children's Hospital.

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Correspondence
Giulio Perrotta
giulio.perrotta@pm.univpm.it

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MATERIALES Y MÉTODOS: Se revisaron artículos originales relacionados con omega-3/omega-6, crecimiento y nutrición en humanos, en pacientes atendidos en los servicios de Ginecología y Pediatría. La revisión de artículos se llevó a cabo en la base de datos de PubMed, desde enero de 1979 hasta marzo de 2023.

RESULTADOS: Se encontraron 44 artículos relacionados con el tema. Surgieron importantes cuestiones críticas respecto a los estudios publicados, a pesar de la evidencia alentadora de la utilidad de los omega-3/omega-6 durante el embarazo, la lactancia, los estados de desnutrición y los procesos inflamatorios, mientras que los datos de la eficacia en el feto, neonatal, y los pacientes pediátricos son conflictivos. En los estudios surgen preguntas estructurales y funcionales que pueden poner en duda la validez de los resultados.

CONCLUSIONES: Los datos son alentadores y sugieren que ciertos aspectos respecto al tipo de administración y dosis de suplementación con ácidos grasos omega-3/omega-6 deben investigarse a mayor detalle para demostrar la validez clínica de dichas prescripciones, especialmente en términos de maduración gestacional, crecimiento y nutrición humana en la práctica clínica en Ginecología y Pediatría.

PALABRAS CLAVE: Ácido docosahexaenoico; Ácido eicosapentaenoico; Omega 3; Omega-6; Feto; Prematuro; Niño; Suplemento dietético.

BACKGROUND

Omega-3/Omega-6

Fatty acids are aliphatic monocarboxylic acids derived from or contained in esterified form in a vegetable or animal fat, oil, or wax, and are divided into short-chain (SCFA), medium-chain (MCFA), long-chain (LCFA), or very long chain (VLCFA), depending on the number of carbon atoms present.[1] α-linoleic acid (ALA), cervonic or docosahexaenoic acid (DHA), and thymnodonic or eicosapentaenoic acid (EPA) are among the major fatty acids of the omega-3 group, which, together with arachidonic acid (AA) of the omega-6 group, are generally considered to be potent anti-inflammatory antioxidants and immunomodulators, which are especially important for brain development, cognitive performance, and the immune system[2-3] and if deficient during pregnancy or lactation can have adverse effects on the unborn child.[4-5] Specifically, several sources of information suggest that humans evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFAs) of ~ 1, whereas in Western diets the ratio is 15/1-16.7/1. Western diets are deficient in omega-3 fatty acids and have excessive amounts of omega-6 fatty acids compared with the diet on which humans evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFAs) and a very high omega-6/omega-3 ratio, as found in current Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, while increased levels of omega-3 PUFAs (a low omega-6/omega-3 ratio) cause suppressive effects.[2]

Fatty acids belonging to the omega-3 group (such as ALA and AA)[6] and omega-9 group (such as OLA)[7] should also be juxtaposed with the omega-3 group, again for their antioxidant and anti-inflammatory properties. Introductory sources can be both animal (animal oils and

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fats, fish oil, especially cod liver, herring and oily fish, salmon, and in lesser amounts in cod, trout, and human milk)[8] and plant sources (corn seed oil, sunflower oil, nuts, transgenic Camelina sativa seed oil (CSOs),[9-10] blueberries,[11] and microalgae,[12] both in natural and synthetic forms. In particular, n-3 PUFAs of marine and plant origin have different effects on erythrocyte fatty acid composition and regulation of glycolipid metabolism.[13]

However, the exact dose to be administered has not been determined, although there are studies that emphasize both personalization of therapy (as is the case with individuals with obesity, who may be affected by different assimilation/absorption due to their clinical condition)[14] and use at night, in that in the absence of dietary intake of EPA and DHA, circulating levels of these fatty acids decrease during the nighttime period and reach their lowest point in the morning, and therefore, overnight consumption of n-3 PUFAs, which counteracts this pattern, may have functional significance.[15] One study went on to focus on the assumption that omega-3 (n-3) fatty acid (FA) supplements increase blood concentrations of EPA and DHA and that most supplements on the market are esterified to triglycerides (TG) or ethyl esters (EE), which limits their absorption and may cause gastrointestinal side effects. Specifically, the 24-hour plasma EPA values were ~2-fold and ~1-fold higher after esterification than the EE and TG forms of n-3 FA, respectively ($P \leq 0.0027$). The effects of the EE and TG treatments did not differ. The 3 supplements had similar side effects of belching, dysgeusia, abdominal discomfort, nausea, and bloating. With this in mind, and intending to compare the 24-hour plasma concentrations of EPA, DHA, and EPA+DHA when provided esterified in monoglycerides (MAG), this study showed that the plasma concentration of n-3 FA in adults is higher after acute supplementation with n-3 FA esterified in MAG than in EE or TG, suggesting that with a lower dose of n-3 FA MAG, the plasma concentrations of n-3 FA achieved are similar to those achieved after higher doses of n-3 FA esterified in EE or TG.[16]

Omega-3/omega-6 and pregnancy

In the literature, supplementation of these fatty acids is so often linked to increased weight gain (of the gestating mother) and a better fetal growth/duration of gestation ratio,[17-20] although there is no lack of contrary studies.[21] Discordance there is, on the other hand, concerning the risk of preterm birth in case of their deficiency: some studies affirm the lack of correlation,[20,22] while others confirm both the risk of preterm birth and placental damage.[23] However, it was also found that: preterm birth < 37 weeks and early delivery < 34 weeks were reduced in women receiving omega-3 LCPUFAs compared with those not receiving omega-3 LCPUFAs; the risk of perinatal death and admission to neonatal care was probably reduced; the risk of low birth weight (LBW) infants was reduced; the risk of large for gestational age (LGA) infants was slightly increased with omega-3 LCPUFA supplementation. Thus, it was shown that omega-3 LCPUFA supplementation during pregnancy is an effective strategy to reduce the incidence of preterm births, although it probably increases the incidence of post-term pregnancies.[24]

Another study claims that maternal DHA supplementation in pregnancy can reduce placental inflammation and differentially modulate nutrient transport capacity in the placenta, mitigating the adverse effects of maternal obesity on placental function,[25] while another study states that DHA supplementation has no significant impact on the neurological development of offspring at 12 months of age,[26] unless there is combined DHA/Choline supplementation and this affects the neurological development of the hippocampus[27] (however, this statement refers only to the "rat" animal model and thus may be considered for possible future studies in human models).

Omega-3/omega-6 and preterm

Concerning neurological and cognitive development, one study found that AA and DHA supplementation, at low doses, results in no improvement [21], while high doses of DHA/EPA can cause serious damage, inducing preterm delivery, prolonged gestation, and hemorrhagic episodes.[28]

Preterm infants who miss the peak period of DHA accretion in the brain during the last trimester of pregnancy (being an important component of neural lipids that accumulate in brain tissue during development),[29] precisely because of their clinical condition also exhibit altered gut microbial composition, partly compensated by omega-3 supplementation, which prompted in the next two weeks by dietary supplementation result in the increase of short-chain fatty acid-producing bacteria (SCFA), such as Bacteroides, Enterobacteriaceae, Veillonella, Streptococcus, and Clostridium.[30]

Recent studies, again in the premature, have then shown that supplementation of DHA, and also in some cases AA, in a combined DHA/AA ratio,[31] significantly improves infant psychomotor and visual development (but without significant effects on global IQ assessed in later years of life.[32] It also improves the cognitive function of attention[33] but not concerning language.[34]

Also, in premature, fatty acid administration can limit retinopathic damage[35] and prevent necrotizing enterocolitis,[36] but does not seem to improve already manifested allergic symptoms[37] despite having a direct correlation with the onset of allergic disease, with protective effects.[3]

The same argument also applies to the hypothesis of bronchopulmonary dysplasia at 36 weeks postmenstrual age,[38] although one study states the opposite, i.e., that due to the reduction of interleukins 1-beta and 6 in serum, the intake provides benefits on symptoms, provided the preterm is very premature.[39]

This paper aims to verify the state of the art on the utilization of omega-3/omega-6 type fatty acids, either through diet or supplementation by supplementation, in the preterm maternal and neonatal population to assess the impact on the health of pregnant women and outcomes on the growth and neurodevelopment of the preterm infant.

MATERIALS AND METHODS

We searched in PubMed until March 30, 2023, for meta-analyses, clinical trials and randomized controlled trials, using the keywords "omega-3/omega-6 fatty acids", "DHA/EPA/ALA/AA", "pregnancy", the fetus" and "preterm", content on the abstract and title have been selected 10,675 useful results, of which 44 original articles were used for the present review as they focused on the topics of growth and neurodevelopment. A single reference (book) related to the analyzed topic from sources outside PubMed was added in the first note. Simple reviews, opinion contributions, or publications in popular volumes were excluded because they were irrelevant or redundant for this paper, and publications that did not present results or statistical samples but only research protocols and proposals, those that did not specifically address the topic of investigation, those with contradictory data, unreliable data, or otherwise with a deficient research design. The search was not limited to English-language articles. No limit was placed on the year of publication, covering the time window from January 1979 until March 2023. **Figure 1**[40]

RESULTS

In the literature, the use of omega-3/omega-6 for supplementation purposes for pregnant women appears encouraging, in terms of fetal

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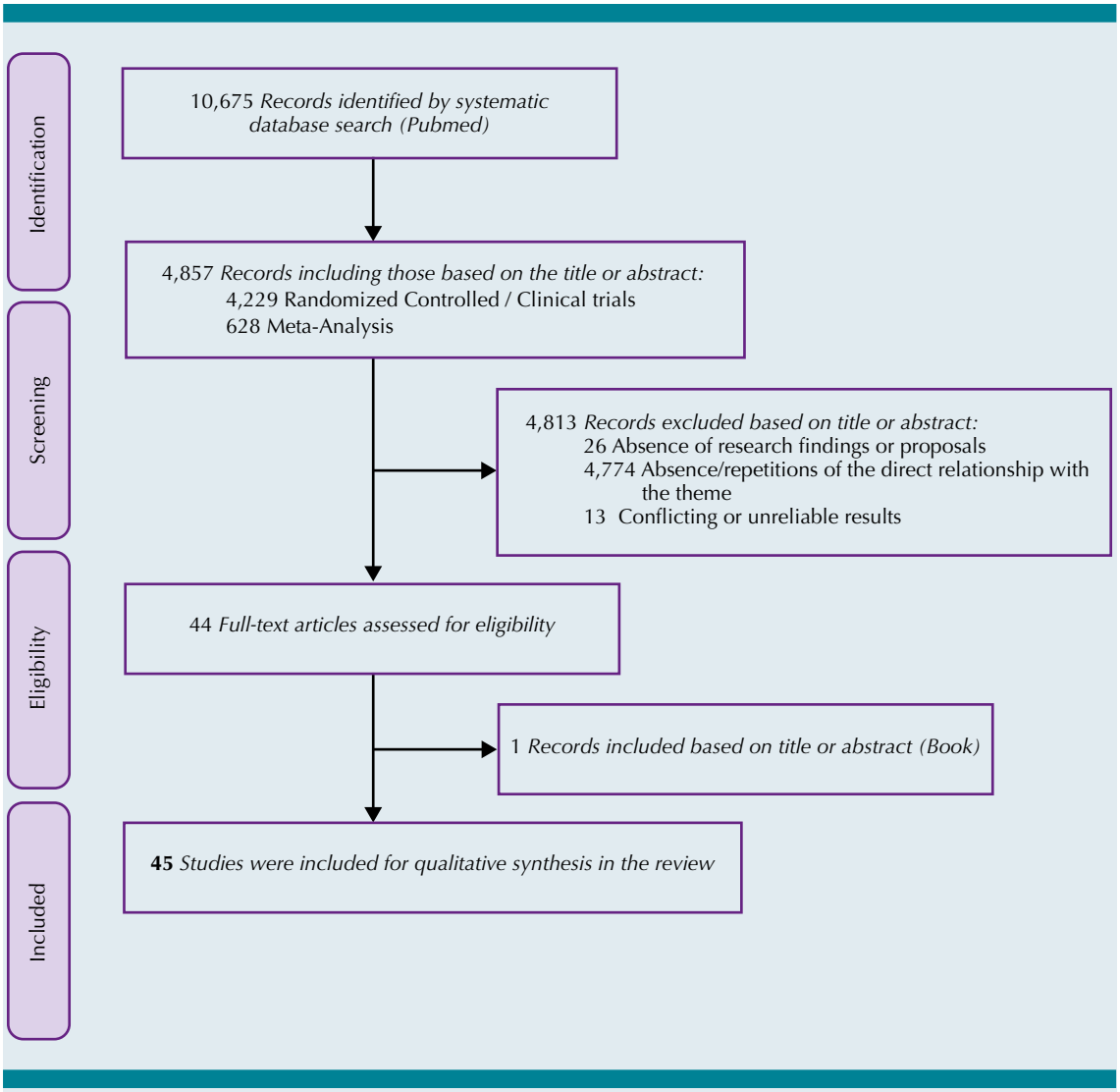

Figure 1. PRISMA flow diagram template for systematic reviews. Adapted from Matthew J. Page *et al.*[40]

growth, maternal weight, and term gestation; in particular, the results show that balanced supplementation based on the patient's medical history, in addition to prescribed drug therapies, improves expected fetal growth outcomes, increasing maternal weight by 5% to 20%, as well as promoting full-term gestation with lower risk of preterm or at-risk births, although there are studies with outcomes to the contrary or otherwise claiming limited benefits in these terms. Differently, however, is the case with preterm infants (with a better health impact if the infant has a gestational age of less than 28 weeks), which although there is encouraging data regarding improvement in certain clinical conditions, such as nonchronic retinopathy damage, bronchopulmonary dysplasia allergic diseases, and necrotizing enterocolitis, due to

the reduction of serum interleukin 1-beta and 6, do not appear to be significantly impacting the neurodevelopment of the infant at 2, 4, and 6 years of age, except with interesting results on the improvement of psychomotor, visual, and cognitive-attentive areas. Further studies then concern the hypothesis of nighttime intake of fatty acids (to the detriment of daytime schedules), the use of alternative sources to animal fats (thus plant-based), and interactions with the gut microbiota/microbiome, which open the door to interesting future scenarios that are certainly encouraging and exciting. **Table 1**

DISCUSSION AND LIMITATIONS

In the literature, the use of omega-3/omega-6 for supplementation purposes for pregnant women and preterm infants is encouraged by the positive outcomes found and the growing interest in intervening in an impactful manner on fetal growth, maternal weight, and full-term gestation, and for preterm infants to boost the chances of recovery of specific and severe clinical hypotheses. However, these exciting findings must be tempered, by several critical issues that have emerged and been noted during this analysis.

Table 1. Cohort studies (Continued on the next page)

Author (year)	Objectives	Type: n	Key results and conclusions
Liu H *et al.* (2022)[13]	Effects of marine-derived and plant-derived omega-3 polyunsaturated fatty acids	R: 180	Perilla oil supplementation reduced FBG, while fish oil supplementation reduced TG level. PUFA n-3s of marine and plant origin have different effects on erythrocyte fatty acid composition and regulation of glycolipid metabolism.
Angoa G *et al.* (2022)[19]	DHA and Very Preterm Infant Growth	R: 528	DHA positively affected the weight profile and neonatal rate of female infants and negatively affected the weight of male infants at 36 weeks of PMA.
Sun L *et al.* (2022)[22]	Omega 3 and preterm birth	Meta: 26	Omega-3 fatty acid supplementation was not associated with a reduced risk of preterm delivery compared with placebo or no treatment during pregnancy.
Simmonds LA *et al.* (2022)[23]	Omega-3 and preterm birth	R: 457	Total n-3 fatty acids in whole blood or plasma can be used to define low pregnancy status and identify women who will benefit most from n-3 LCPUFA supplementation to reduce the risk of preterm delivery.
Fisk ML *et al.* (2022)[14]	Omega-3 and adipose tissue inflammation	R: 84	Reduced expression of genes responsible for fatty acid activation and metabolism may contribute to an inflammatory profile of oxylipins and limit the effects of LC n-3 PUFAs in obesity. Individualized supplementation of LC n-3 PUFAs based on obesity status may be necessary.
Miles EA *et al.* (2021)[3]	DHA/AA and developing immune system	Sys: 111	LCPUFAs play a role in immune development that is of clinical importance, particularly concerning allergic sensitization and allergic manifestations including wheezing and asthma.
Lehner A *et al.* (2021)[4]	Clinical implications of DHA/EPA supplementation on the cognitive parameters	Meta: 11	There is no statistically significant association between DHA/EPA supplementation and assessed cognitive parameters or birth weight.
Aparicio E *et al.* (2021)[5]	DHA/EPA and pregnancy	R: 479	A high level of education, advanced age, consumption of fish and seafood, and/or not smoking are factors that influence a better omega-3 polyunsaturated fatty acid (n-3 PUFA) profile in both trimesters of pregnancy. Further research is needed to investigate these findings and their health consequences.

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Table 1. Cohort studies (Continued on the next page)

Author (year)	Objectives	Type: n	Key results and conclusions
Chevalier L *et al.* (2021)[16]	DHA/EPA and blood concentrations	R: 22	The plasma concentration of n-3 FA in adults is higher after acute supplementation with n-3 FA esterified.
Ivanisevic M *et al.* (2021)[17]	Clinical implications of DHA/EPA supplementation on pregnancy	R: 111	Pregnancy weight gain and concentration and proportions of DHA, PUFA n-3 with a decrease in the proportion of AA, PUFA n-6 and AA/DHA ratio in maternal serum and umbilical vein serum summarize the effect of supplementation with EPA and DHA.
Monthé-Drèze C *et al.* (2021)[18]	Omega-3 and pregnancy	R: 72	Supplementation with n-3 PUFAs in women with overweight/obesity (OWOB) resulted in increased lean mass at birth, improved fetal growth, and longer gestation.
Hellstrom A *et al.* (2021)[35]	Omega-3 and Retinopathy of Prematurity (ROP)	R: 209	Enteral supplementation of AA: DHA reduced the risk of severe ROP by 50% and showed overall higher serum levels of both AA and DHA.
Bernabe-Garcìa M *et al.* (2021)[36]	Omega 3 and Necrotizing Enterocolitis in Preterm Infants (NEC)	R: 214	A daily dose of DHA for 14 days, starting from the first enteral feeding, can prevent NEC in preterm infants.
Khairani S *et al.* (2021)[40]	Potential use of a Curcumin-Piperine Combination as an Antimalarial Agent	Sys: 46	New information regarding the development of a curcumin-piperine combination for future malaria therapy
Hewawasam E *et al.* (2021)[33]	Omega-3 and preterm	R: 120	Enteral DHA supplementation did not result in improved attention in children born preterm at 18 months of corrected age.
Tomaszewski N *et al.* (2020)[42]	DHA/EPA and APOE Genotype	R: 275	The lower increase in plasma DHA/AA and EPA/AA in APOEε4/ε4 carriers after DHA supplementation reduces brain intake and affects the efficacy of DHA supplementation.
Chen H *et al.* (2020)[43]	DHA/EPA vs ALA on cardiometabolic disorders	Meta: 14	Dietary supplementation of EPA/DHA improved TG and HDL status but increased LDL levels compared with ALA.
Brainard JS *et al.* (2020)[6]	Omega-3, Omega-6, and Polyunsaturated Fat for Cognition	Meta: 38	Long-chain omega-3 probably has little or no effect on new neurocognitive outcomes or cognitive impairment.
Jackson PA *et al.* (2020)[15]	Diurnal rhythm of plasma EPA and DHA in healthy adults	R: 21	In the absence of dietary intake of EPA and DHA, circulating levels of these fatty acids decrease during the overnight period and reach their lowest point in the morning. Consumption of n-3 PUFAs at night, which counteracts this pattern, may have functional significance.
Khandelwal S *et al.* (2020)[26]	DHA and neurodevelopment	R: 957	Supplementing mothers during pregnancy and lactation with 400 mg/day of DHA had no impact on the neurological development of the offspring at 12 months of age.
von Schacky C *et al.* (2020)[28]	DHA and pregnancy	R: 680	Very high intake or levels of EPA and DHA can also produce health problems, such as bleeding, prolonged gestation, or even premature delivery.
Gawlik NR *et al.* (2020)[34]	Influence of DHA supplementation during pregnancy on language development across childhood	R: 726	Evidence of an effect of prenatal DHA supplementation on language abilities across childhood is negligible and could be a chance finding.

Table 1. Cohort studies (Continued on the next page)

Author (year)	Objectives	Type: n	Key results and conclusions
Marc I *et al.* (2020)[38]	DHA and Bronchopulmonary Dysplasia	R: 255	Among preterm breastfed infants born before 29 weeks of gestation, maternal DHA supplementation during the neonatal period did not significantly improve bronchopulmonary dysplasia-free survival at 36 weeks postmenstrual age compared with placebo.
Gunaratne AW *et al.* (2019)[37]	Omega-3 and symptoms of allergic disease	R: 569	High-dose DHA supplementation in infants born at <33 weeks' gestation did not alter symptoms or severity of allergic disease at 7 years or from birth to 7 years compared with standard-dose DHA.
Hsiao C-C *et al.* (2019)[39]	LCPUFA and bronchopulmonary dysplasia (BPD) in very premature infants	R: 60	In very premature infants, early administration of LE-containing fish oils significantly reduced IL-1β and IL-6 levels in serum and BALF and was associated with a shorter duration of ventilatory support and less BPD.
Ingol TT *et al.* (2019)[21]	DHA/AA and Growth/ Adiposity	R: 377	Among children born preterm, daily supplementation with DHA + AA for 180 days produced no short-term differences in growth or adiposity compared with placebo. If DHA supplementation is implemented after the first year of life, it can be expected not to affect short-term growth or adiposity.
West AL *et al.* (2019)[9]	DHA/EPA in CSO	R: 36	The incorporation into blood lipids of EPA and DHA consumed in the form of transgenic CSOs was equivalent to that of commercial blended fish oil (BFO) and such transgenic vegetable oils are an adequate dietary source of EPA and DHA in humans.
Yang J *et al.* (2019)[8]	DHA/EPA and oxidative stress	M: 21	It remains controversial whether n-3 PUFAs are effective in counteracting oxidative stress. On the other hand, data suggest that n-3 PUFA supplementation may be effective in the early stages of hepatic steatosis (NAFLD), but not in patients with more severe NAFLD or non-alcoholic steatohepatitis (NASH).
Schwab US *et al.* (2018)[10]	Camelina Sativa Oil (CSO)	R: 79	A diet enriched in CSO improves serum lipid profile as compared with a diet enriched in FF or LF in subjects with impaired fasting glucose, with no differences in glucose metabolism or concentrations of inflammatory markers.
McNamara RK *et al.* (2018)[11]	Omega-3 and blueberry (BB)	R: 65	The FO and BB groups reported fewer cognitive symptoms, and the BB group showed better memory discrimination, indicating that supplementation improved cognition. The cognitive benefit in the BB group was associated with the presence of urinary anthocyanins reflecting recent BB intake but not anthocyanin metabolites. However, combined FO + BB treatment was not associated with cognitive improvement as expected.
Dawczynski C *et al.* (2018)[12]	Omega-3 and treatment of rheumatoid arthritis (RA)	R: 38	DHA supplementation with microalgae improves disease activity in patients with RA along with a shift in the balance of AA- and DHA-derived lipid mediators toward an anti-inflammatory/pro-remedial state

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Table 1. Cohort studies (Continued on the next page)

Author (year)	Objectives	Type: n	Key results and conclusions
Middleton P *et al.* (2018)[24]	Omega-3 fatty acid addition during pregnancy	Meta: 70	In the overall analysis, preterm delivery < 37 weeks and early delivery < 34 weeks were reduced in women receiving omega-3 LCPUFA compared with those not receiving omega-3 LCPUFA. The risk of perinatal death and hospitalization in neonatal care was likely reduced, the risk of low birth weight (LBW) infants was reduced, and the risk of infant large for gestational age (LGA) infants was slightly increased with omega-3 LCPUFA intake.
Mulder KA *et al.* (2018)[29]	Fetal DHA inadequacy and the impact on child neurodevelopment	R: 98	Inadequate DHA during gestation may impair the child's development, but it is not known whether there are any lasting effects, although maternal DHA status is positively correlated with children's performance on some tests, including language and short-term memory.
Jiang T *et al.* (2018)[30]	Omega-3 and infant intestinal microbiome	R: 173	A significant association was found between specific dietary fatty acid with stereospecifically numbered sn-2 position (sn-2 FA) in milk and the infant's gut microbiota between decanoic acid (C10:0), myristic acid (C14:0), stearic acid (C18:0), C16:0, AA (C20:4 n-6), DHA (C22:6 n-3) with Bacteroides, Enterobacteriaceae, *Veillonella, Streptococcus*, and *Clostridium*. These microbes were involved in SCFA production and other functions and increased significantly at 13-15 days after the start of breastfeeding.
Lager S *et al.* (2017)[25]	DHA and pregnancy	R: 73	Maternal DHA supplementation in pregnancy reduces placental inflammation and differentially modulates nutrient transport capacity in the placenta and may mitigate the adverse effects of maternal obesity on placental function.
Shulkin M *et al.* (2018)[32]	Omega-3 and childhood psychomotor and visual development	Meta: 38	N-3 PUFA supplementation improves childhood psychomotor and visual development, without significant effects on global IQ later in childhood.
Rajarethnem HT *et al.* (2017)[27]	DHA and Choline	R: 40	Combined choline and DHA supplementation during normal pregnancy improve fetal hippocampal neurodevelopment better than choline or DHA supplementation alone.
Scholtz SA *et al.* (2015)[44]	DHA/AA and FADS genotypes	R: 205	DHA reduced the AA status of homozygotes of minor alleles of both FADS SNPs but not of homozygotes of major alleles at the time of delivery. Any physiological effect of changing the DHA/AA ratio by increasing DHA intake appears to be greater in homozygotes of minor alleles of some FADS SNPs.
Schwingshackl L *et al.* (2014)[7]	Monounsaturated fatty acids, olive oil and health status	Meta: 42	The results indicate an overall risk reduction of all-cause mortality (11%), cardiovascular mortality (12%), cardiovascular events (9%), and stroke (17%) when comparing the top versus bottom third of MUFA, olive oil, oleic acid, and MUFA: SFA ratio. MUFA of mixed animal and vegetable sources per se did not yield any significant effects on these outcome parameters. However, only olive oil seems to be associated with reduced risk. Further research is necessary to evaluate specific sources of MUFA (i.e. plant vs. animal) and cardiovascular risk.

Table 1. Cohort studies (Continuation)

Author (year)	Objectives	Type: n	Key results and conclusions
Carlson SE *et al.* (2013)[20]	DHA and pregnancy outcomes	R: 350	Supplementation of 600 mg DHA/day in the last half of gestation resulted in longer gestation duration and larger baby size. A reduction in early preterm and very low birth weight could be important clinical and public health outcomes of DHA supplementation.
van Good SA et al (2010) [31]	DHA/AA and general movements	R: 119	The overall quality of movement at 12 weeks is sensitive to maternal dietary DHA/AA ratio.
Simopoulos AP *et al.* (2002) [2]	The importance of the ratio of omega-6/omega-3 essential fatty acids	Sys: 101	A lower ratio of omega-6/omega-3 fatty acids is more desirable to reduce the risk of many of the high-prevalence chronic diseases in Western societies, as well as in developing countries, that are exported to the rest of the world.

Meta: Meta-analysis; Sys: Systematic review; R: Randomized Study.

In fact, most of the published studies suffer from several shortcomings, both structural and functional, which emerge precisely from their research design and implementation; specifically: a) major structural deficiencies, such as frequent small sample sizes for each category evaluated; b) questionable quality of the included studies or possible conflicts of interest, for commercial reasons; c) technical errors (as in the case of the study adding curcumin to omega-3 supplementation but not taking into account the fact that it requires piperine to be activated or the lack of knowledge of the exact doses to be administered or the interaction between fatty acids, foods, and pharmacological products); d) the difficulty of reliably measuring cognitive performance in childhood patients; and e) the non-comparability of blood levels of omega-3 long-chain polyunsaturated fatty acids; f) the possible influence of environmental and genetic factors (such as in the case of the presence of the APOEε4 -APOE4- allele that accelerates the oxidation of omega-3 polyunsaturated fatty acids -PUFAs- or in the hypothesis of the minor allele rs3834458 in FADS2 that results in lower delta-6 desaturase activity resulting in increased ALA and decreased EPA, DPA, and DHA in the blood); g) the absence of recognized and agreed international guidelines about the exact maximum administration and dosage (effectively leaving wide discretion to the clinician or investigator); h) the pharmacological profiles that interact in the therapeutic plan with fatty acid administration; i) the quality of the fatty acids selected and administered.[41-46] These limitations, therefore, can significantly affect the often-agreed conclusion that studies do not show a statistically significant association between DHA/EPA supplementation and assessed cognitive parameters or birth weight, as well as may undermine the reliability of the results obtained to an alleged advantage in administering.

In the **Table 2** showed the clinical message, as the final result of the literature search.

CONCLUSION

Significant critical issues emerge concerning published studies, despite encouraging evidence regarding the usefulness of omega-3/omega-6 used during pregnancy, lactation, in states of malnutrition and inflammatory-based processes, while data regarding effective use in fetal, neonatal, and pediatric patients are conflicting. The noted structural and functional shortcomings of the samples studied lead to the inference that such correctives could ensure a better perception of the phenomenon, also taking into account

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Table 2. Clinical message

Scope	Clinical message
Administration to pregnant women	The data are encouraging, but the studies are often not very robust, having small selected populations, missing data related to doses and type of administration, and administration outcomes can be explained by more robust statistical models. However, data on fetal growth, maternal weight, and term gestation appear interesting (albeit with discrepancies regarding placental damage in high-dose DHA/EPA administrations)
Administration to preterm infants	Data are often incomplete and explained by weak statistical models. There is insufficient information regarding the neurodevelopment of the preterm infant to be able to express a positive outcome with certainty, although there is no shortage of useful findings regarding improvement in the psychomotor, visual, and cognitive-attentive areas, in the absence of guidelines on the mode of administration and maximum dosage that can be administered (thus leaving wide discretion to the investigator and clinician)
Hypothesis of administration utility	The administration of fatty acids, albeit with significant variations in the mode and amount of dosing, is useful and encouraging for the treatment of certain morbid conditions, although data in these studies regarding pharmacological administrations during the study period are lacking (and thus possible co-effects cannot be discriminated): retinopathic damage, bronchopulmonary dysplasia, allergic disease, and necrotizing enterocolitis, due to the reduction in serum interleukin 1-beta and 6

that the hypothetical assumption of almost all studies is that fatty acid supplementation can have a curative effect on already active diseases, whereas in reality such prescriptions should be considered as adjuvant therapies to prevent or promote symptomatic regression, precisely because of their anti-inflammatory, antioxidant and immunomodulatory virtues. Future research is expected to solve some critical questions with better approaches to answer how omega-3/omega-6 fatty acid supplementation can contribute to better human growth and nutrition in the clinical practice of Gynecology and Pediatrics.

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