Are There Changes in the Fatty Acid Profile of Breast Milk with Supplementation of Omega-3 Sources? A Systematic Review

Existem mudanças no perfil de ácidos graxos no leite materno com a suplementação de fontes de ômega 3? Uma revisão sistemática

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Abstract

Purpose To evaluate the effect of supplementation with omega-3 sources on the fatty acid composition of human milk.
Methods The review consisted of the search for articles published in PubMed, Biblioteca Virtual de Saúde (Virtual Health Library[VHL]) and Web of Science databases using the following keywords: *fatty acids*, *omega-3*, *human milk* and *supplementation*; for this purpose, we have used the program of research to integrate the services for the maintenance of autonomy (PRISMA) checklist. The following selection criteria were used: articles in English, Portuguese, Spanish or Italian, published between 2000 and 2015, and about studies performed in humans. We found 710 articles that met the established criteria; however, only 22 of them were selected to be part of this study.
Results All studies found a positive relationship between the consumption of omega-3 sources and their concentration in human milk. The differences in the findings are due to the distinct methods used, such as the specific time of the omega-3 supplementation, the type of omega-3 source offered, as well as the sample size.
Conclusion Although the studies were different in several methodological aspects, it was possible to observe the importance of omega-3 supplementation during gestation and/or the puerperium.

Keywords
- ► pregnant women
- ► breastfeeding
- ► human milk
- ► omega-3 fatty acids
- ► systematic review

Resumo

Objetivo Avaliar o efeito da suplementação com fontes de ômega 3 sobre a composição de ácidos graxos do leite humano.

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Métodos A revisão consistiu na busca de artigos publicados nas bases de dados PubMed, Biblioteca Virtual de Saúde e *Web of Science* utilizando-se as palavras-chave: *ácidos graxos*, *ômega-3*, *leite materno* e *suplementação*; para isso, foi utilizado o checklist PRISMA. Foram utilizados os seguintes critérios para a seleção: artigos publicados em inglês, português, espanhol ou italiano, entre os anos de 2000 a 2015, sobre estudos realizados em humanos. A busca bibliográfica, segundo a estratégia estabelecida, resultou em 710 artigos. Entretanto, apenas 22 destes foram selecionados para compor a presente revisão.

Resultados Todos os estudos encontraram relação positiva entre o consumo de fontes de ômega 3 e sua concentração no leite humano. As diferenças nos achados se devem aos métodos empregados como, por exemplo, o momento da suplementação do ômega 3, o tipo de fonte de ômega 3 ofertado, e o tamanho amostral.

Conclusão Apesar de os estudos serem díspares em inúmeros aspectos metodológicos, observou-se a importância da suplementação do ômega 3 na gestação e/ou no puerpério.

Palavras-chave
- gestantes
- aleitamento materno
- leite humano
- ácidos graxos ômega-3
- revisão sistemática

Introduction

The importance of polyunsaturated fatty acids of the omega-3 (ω-3) series (docosahexaenoic acid [22:6 ω3, DHA] and eicosapentaenoic acid [20:5 ω3, EPA]) in the development of the fetal brain, as well as in the cognitive and visual acuity of the child, is widely recognized. These fatty acids are part of the composition of the cell membranes and the nervous system, especially DHA, which is preferentially transported by the placenta to the fetus and provides important components to the phospholipid membrane.[1,2]

The amount of fatty acids in human milk (HM) depends on maternal stocks, dietary intake and synthesis thereof in the mammary glands.[3] The concentration of DHA varies specifically, probably due to the woman's feeding habits, since its synthesis in the mammary gland is minimal.[1,2,4] During gestation and lactation, this synthesis is limited by the fetus. For this reason, numerous studies have been conducted to evaluate the effects of the supplementation of this fatty acid on the composition of HM .[4,5] Other facts to be taken into consideration are that the concentration of DHA in HM decreases as lactation progresses, and that supplementation during lactation raises DHA concentrations in breast milk.[6]

The study conducted by Bortolozo et al (2013)[2] aimed to evaluate the impact of omega-3 fatty acid supplementation between the third trimester of pregnancy and the third month after delivery, and its influence on the composition of HM. Although no statistical difference was found in the total lipid values between the studied groups, the milk of mothers supplemented with fish oil had higher concentrations of DHA and EPA, demonstrating that a higher consumption of omega-3 may influence its concentration in HM.[2] However, the results on the effects of omega-3 supplementation during gestation are still contradictory.[4]

Due to the controversies between the studies, as well as to the importance of the theme for the health of the newborn, this systematic review aims to evaluate the studies that verified the effects of omega-3 supplementation during pregnancy and/or the puerperium on the composition of HM. The bibliographical survey of this theme aims to assist the maternal and infant populations, together with health professionals, to determine the importance of supplementation, offering subsidies for its practice.

Methods

A systematic review of the available literature consisted of a retrospective search of scientific articles that aimed to evaluate the composition of HM after supplementation with omega-3 fatty acids.

The following bibliographic databases have been used: PubMed, Biblioteca Virtual da Saúde (Virtual Health Library [VHL]) and Web of Science. The search for the articles was performed independently by two researchers, and it began in August and ended in October of 2015. The selected studies were published during the period comprised between 2000 and 2015. The following keywords were used in the search strategy: ***fatty acids***, ***omega-3***, ***human milk*** and ***supplementation***.

The bibliographic search was performed according to the established strategy, and resulted in 710 articles. A total of 163 articles were found in the VHL database; however, after reading the abstracts, we have selected 11 thereof; 239 articles were found in the PubMed database; however, we have only selected 21of these; and 308 articles were found in the Web of Science database, from which we have selected 2 articles. Thus, a total of 22 articles have been selected to compose the present study, reiterating that there were 12 articles replicated in the analyzed databases. The others were suppressed for the following reasons: discussion of different associations between omega-3 and HM, such as allergy, visual acuity and growth; literature reviews; studies replicated across different databases; studies published in other languages and/or that were were not available in their entirety. We used a checklist with 27 items and a 4-step flowchart, advocated by PRISMA,[7] which aims to help authors improve the reporting of systematic reviews.

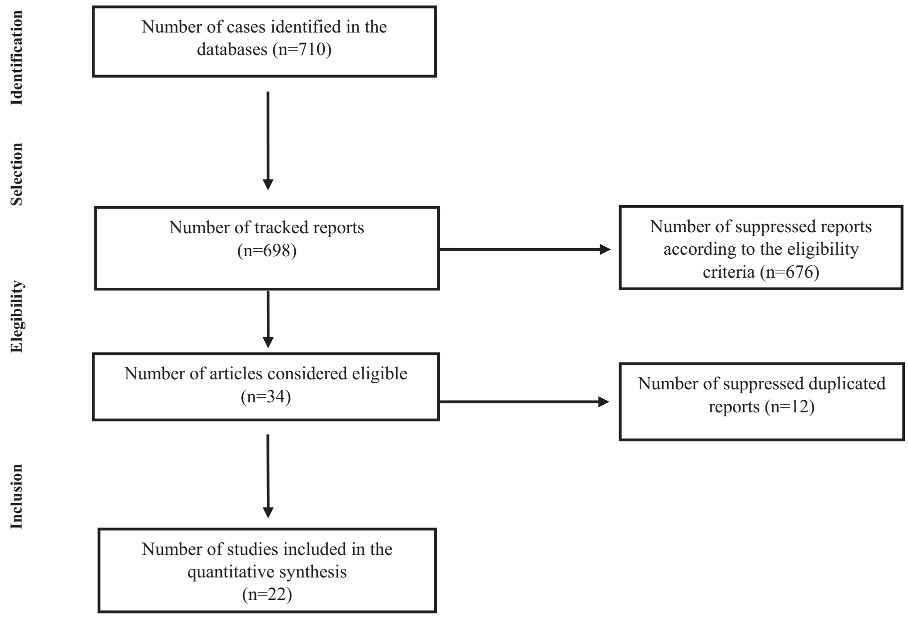

Fig. 1 Flowchart of the selection process for selected articles – PRISMA.

Therefore, a summary of each stage of the selection process of articles that composed this systematic review was arranged in the Flowchart (►**Fig. 1**).

The criteria used in the selection of articles for the review included language (Portuguese, English, Spanish and Italian) and year of publication (2000 to 2015).

The selected articles were compared in relation to the following parameters: year of publication, country of origin, sample size, average age of participants, type of design, rate of follow-up losses, period in which the woman and the milk have been evaluated, omega-3 supplementation period, type of supplement, amount offered, omega-3 evaluation methods, confounding factors controlled in the analysis, estimators used in the statistical analysis, and main results observed.

Results

Once the established strategy was put into practice, 22 articles were selected by bibliographic search to compose the present revision. Four were originated in the United States, one in Canada, one in Denmark, three in Brazil, three in Australia, three in Chile, one in Israel, one in Iceland, one in Mexico, two in Germany, and two in the Netherlands. Regarding the age groups, the majority of the articles (18) only reported the average age of the participants. Regarding language, two articles were written in Spanish, one in Portuguese and the remaining ones in English (►**Table 1**).

As for the design employed, intervention studies were used in most cases, and there was only one observational study. Information on follow-up losses were obtained from 21 studies. The losses ranged from 0 to 78%. The results among the studies, regarding the period of evaluation of the woman and the milk, were quite dissimilar. Regarding the period of supplementation, it was observed that 12 studies evaluated supplementation in infants, 7 in pregnant women, and only 3 evaluated supplementation both in pregnancy and in the puerperium (►**Table 2**).

In regards to the type of supplement or food offered to the participants, 3 studies used dairy supplements, 16 provided DHA-rich oils (such as, tuna, single-celled algae, cod, flaxseed), 2 supplied fish (sardine and jure) and 1 study performed food education to increase the consumption of fish sources. As for the method to evaluate the amount of omega 3 in HM, it was observed that all the studies used chromatography. The DHA value ranged from 170 mg to 2,200 mg per day (►**Table 3**).

Among the 22 selected articles, 9 did not evaluate the consumption of omega-3 food sources. Among those who reported it, the majority (32%) used the food frequency questionnaire (FFQ). Regarding the estimators, it was observed that nine studies used the average, seven used the correlation index, five the median and only one study used the combination of correlation index with the average. Regarding the exclusion criteria, nine articles did not mention them in the methods (►**Table 4**).

Regarding supplementation, all studies found a positive relationship between the consumption of omega-3 sources and their concentration in HM, therefore, highlighting the importance of supplementation of these fatty acids during pregnancy and/or puerperium, which translates into positive results in both cognitive development and visual acuity.

Discussion

The omega-3 and omega-6 polyunsaturated fatty acids consumed through dietary triglycerides are digested in the small intestines and can then be absorbed, transported into the bloodstream and taken up between tissues throughout the body (including brain, retina and heart).[8] Essential dietary

Table 1 Year of publication, origin, sample size, and age of the participants of the selected studies on the fatty acid profile of breast milk with the supplementation of omega-3 sources, 2000–2015

Authors	Pub year	Country	Sample (n)	Age (years)
Atalah et al[5]	2009	Chile	352 pregnant women	Intervention group 26.7 and control group 25.0 (average)
Bergmann et al[38]	2008	Germany	144 pregnant women	30.7 (average)
Boris et al[27]	2004	Denmark	44 pregnant/ puerperal women	NI
Bortolozo et al[2]	2013	Brazil	80 pregnant/ puerperal women	25.0 (average)
Dunstan et al[20]	2007	Australia	98 pregnant women	NI
Fidler et al[17]	2000	Germany	10 puerperal women	30.6 (average)
Francois et al[36]	2003	United States	9 puerperal women	28.0 to 39.0
Gaete and Atalah[1]	2003	Chile	26 puerperal women	26.9 (average)
Gaete, Atalah and Araya[31]	2002	Chile	28 puerperal women	Intervention group 25.6 and control group 26.4 (average)
van Goor et al[39]	2009	Netherlands	182 pregnant/ puerperal women	32.4 (average)
Hawkes et al[40]	2001	Australia	120 puerperal women	30.2 (average)
Imhoff-Kunsch et al[13]	2011	Mexico	1,094 pregnant women	26.0 (average)
Jensen et al[18]	2000	United States	26 puerperal women	29.2 (average)
Marc et al[32]	2011	Canada	32 puerperal women	Intervention group 27.2 and control group 26.9 (average)
Olafsdottir et al[41]	2006	Iceland	77 puerperal women	31.0 (average)
Patin et al[35]	2006	Brazil	31 puerperal women	27.9 (average)
Ribeiro et al[30]	2012	Brazil	51 pregnant women	20.0 to 30.0
Sherry et al[42]	2015	United States	89 pregnant women	29.0 (average)
Smit et al[37]	2000	Israel	26 puerperal women	23.5 (average)
Smithers et al[43]	2010	Australia	121 puerperal women	30.0 (average)
Valentine et al[44]	2013	United States	21 puerperal women (donors)	31.0 (average)
Weseler et al[45]	2008	Netherlands	52 pregnant/ puerperal women	31.7 (average)

Abbreviation: NI, Not informed.

Table 2 Type of design, losses, period of evaluation and supplementation of sources of omega-3, 2000–2015

Authors	Design	Losses (%)	Period in which the women were evaluated	Period in which the milk was evaluated	Period of supplementation of omega-3 fatty acids
Atalah et al[5]	Clinical trial	70.0	Three times during gestation and once in the second month after delivery	2nd month after childbirth	During pregnancy
Bergmann et al[38]	Randomized double blind clinical trial	45.8	21st and 37th weeks of gestation, at delivery, and 1 and 3 months after delivery	3rd month after childbirth	21st to 37th week, continuation was optional
Boris et al[27]	Randomized clinical trial	18.2	30th gestational week and the 1st month after delivery	4th, 16th and 30th days after childbirth	From the 30th gestational week until delivery (group 1) or until the 30th day after delivery
Bortolozo et al[2]	Randomized controlled clinical trial	25.0	Last trimester of pregnancy until the 3rd month of lactation	30th, 60th, 90th days after childbirth	Last trimester of pregnancy (baseline) until the 3rd month of lactation
Dunstan et al[20]	Randomized double blind clinical trial	25.0	3rd and 6th days, and 6th month after childbirth	3rd and 6th days, and 6th month after childbirth	20th week of gestation until delivery
Fidler et al[17]	Randomized clinical trial	0.0	From the 4th week until the 6th after delivery	In the 4th week after delivery (before starting supplementation), at the 6th week after delivery (after supplementation), and at 6, 12, 24, 36 and 48 hours after intake of the supplement	From 4 to 6 weeks after delivery (14 days)
Francois et al[36]	Clinical trial	22.0	10 weeks: 2 weeks of washout* at baseline (to stabilize the omega-6 and 3 intakes); 4 weeks of linseed oil supplementation and 4 weeks after supplementation	1 sample at baseline, 1 sample after washout* (2 weeks after the start of study), 4 samples at weekly intervals during 4 weeks of supplementation, and 4 samples at weekly intervals during the post-supplementation period (4 weeks).	4 weeks
Gaete and Atalah[1]	Cohort	7.69	From entry into the study until the 2nd week after food education	2 weeks after food education	Food education on the day of study entry
Gaete et al[31]	Randomized clinical trial	17.2	From the study entry to the 15th day after intervention	15 days after intervention	15 days
van Goor et al[39]	Randomized double blind clinical trial	51.6	Registration day up to 12 weeks after delivery	2nd to 12th weeks after delivery	17th week of gestation until the 12th week after childbirth
Hawkes et al[40]	Randomized double blind clinical trial	31.7	3rd day after birth until the end of the 12th week after delivery	In the 4th week after delivery	12 weeks

Table 2 (*Continued*)

Authors	Design	Losses (%)	Period in which the women were evaluated	Period in which the milk was evaluated	Period of supplementation of omega-3 fatty acids
Imhoff-Kunsch et al[13]	Randomized double blind clinical trial	11.0	Gestation (18th to 22nd weeks) until 1 month after delivery	1 month after birth	From the 18th to the 22nd gestational week until delivery
Jensen et al[18]	Clinical trial	7.7	2nd to 8th weeks after delivery	At the 2nd, 5th and 8th weeks after delivery	6 weeks
Marc et al[32]	Clinical trial	25.0	1 postnatal week (between 3 and 7 days) before starting DHA supplementation and at follow-up at 15 days (3 weeks) and 49 days (7 weeks)	First postnatal week (between 3rd and 7th days) before starting supplementation and at follow-up on days 15 and 49	1 week after delivery until term (36 weeks) - > 8–12 weeks of supplementation
Olafsdottir et al[41]	Randomized clinical trial	48.0	2nd and 4th months after delivery	2nd and 4th months after delivery	Registration day up to 4 months after delivery
Patin et al[35]	Clinical trial	NI	0, 15 and 30 days after delivery	0, 15 and 30 days after delivery	1st and 15th days after delivery
Ribeiro et al[30]	Randomized clinical trial	78.4	30th gestational week up to 15 days after delivery	15th day after delivery	15 days (from the 30th gestational week)
Sherry et al[42]	Clinical trial	7.9	From enrollment (4th to 6th weeks after delivery) up to 6 weeks after supplementation	Baseline and 6th week aftersupplementation	6 weeks
Smit et al[37]	Clinical trial	11.0	For one week	Baseline shortly after ingestion of the supplement. On day 1 and day 7 after the intake of the supplement	1 week
Smithers et al[43]	Randomized double blind clinical trial	19.0	During all hospitalization of the preterm newborn	At intervals of 2 weeks during the hospitalization of the newborn	From study entry (delivery < 33 weeks) until the expected date of delivery
Valentine et al[44]	Randomized clinical trial	38.0	3 days before supplementation until 12 weeks post supplementation	0, 7th, 14th, 21st, 28th and 84th days after the supplementation	During all the time they donated milk to the milk bank (from 7–90 days)
Weseler et al[45]	Randomized double blind clinical trial	34.6	Pregnancy (36 weeks) up to the 11th week after delivery	3rd, 5th and 11th weeks after delivery	Gestation (36th week) up to 11th week postpartum

Abbreviation: NI, not informed.
Note: *Washout: time necessary for the concentration of a medicinal product to be negligible after cessation of therapy.

Table 3 Characteristics of the selected studies on the profile of fatty acids in breast milk with omega-3 sources supplementation, 2000–2015

Authors	Type of supplement/food used as source of omega-3	Amount offered	Placebo/control	Method used to evaluate omega-3 intake	Method to evaluate the amount of omega-3 present in HM
Atalah et al[5]	Milk drink made from powdered milk and hydrolyzed cereals enriched with microencapsulated vitamins, minerals and omega-3 fatty acids	60 mg DHA + 14 mg EPA in 200 mL (2 kg/month)	Powdered milk	Food survey	Chromatography
Bergmann et al[38]	Supplement based on acidified and flavored milk	Group 1: Basic supplement plus 4.5 g FOS Group 2: Basic supplement with FOS + 200 mg of DHA	Basic supplement enriched with vitamins and minerals	NI	Chromatography
Boris et al[27]	Fish oil	900 mg DHA + 1300 mg EPA/day	Olive oil	NI	Chromatography
Bortolozo et al[2]	Fish oil	315 mg DHA + 80 mg EPA/day	Maize starch	24h reminder on alternate days of the week, including a weekend day	Chromatography
Dunstan et al[20]	Fish oil	2200 mg DHA + 1100 mg EPA / day	Olive oil	NI	Chromatography
Fidler et al[17]	Oil rich in DHA (DHASCO)[1]	200 mg DHA / day	Mixture of soybean and corn oils	7-day food record	Chromatography
Francois et al[36]	Linseed oil	10.7 g ALA	NI	Food survey	Chromatography
Gaete and Atalah[1]	Food education	NI	NI	Food survey	Chromatography
Gaete et al[31]	Canned fish(horse mackerel)	160 g fish 2 times a week	Regular food	Food survey	Chromatography
van Goor et al[39]	DHA + ARA capsules, DHA capsules	Group 1 = 220 mg DHA + 36 mg EPA + 220 mg ARA + 7 mg ALA + 46 LA Group 2 = 220 mg DHA, 34 mg EPA + 15 mg ARA + 32 mg ALA + 274 LA	Soybean oil	NI	Chromatography
Hawkes et al[40]	Tuna oil	Group 1 = 300 mg DHA + 70 mg EPA/day Group 2 = 600 mg DHA + 140 mg EPA/day	Sunflower seed oil	NI	Chromatography
Imhoff-Kunsch et al[13]	Seaweed oil	400 mg DHA	Olive oil	Food survey	Chromatography

Table 3 (*Continued*)

Authors	Type of supplement/food used as source of omega-3	Amount offered	Placebo/control	Method used to evaluate omega-3 intake	Method to evaluate the amount of omega-3 present in HM
Jensen et al[18]	Group 1: supplement made from algae with a high content of DHA Group 2: eggs with a high content of DHA Group 3: fish oil	Group 1: 230 mg DHA/day Group 2: 170 mg DHA/day Group 3: 260 mg DHA/day	Eggs	NI	Chromatography
Marc et al[32]	Oil rich in DHA (DHASCO)*	1200 mg DHA/ day	No intervention	Food survey	Chromatography
Olafsdottir et al[41]	Cod liver oil	1107 mg DHA + 783 mg EPA/ day	No intervention	24h reminder + additional questions about fish consumption	Chromatography
Patin et al[35]	Fried sardines	4 kg of sardines (2 kg on day 0 and 2 kg on the 15th day)	The study had no control group	24h reminder	Chromatography
Authors	Type of supplement/food used as source ofomega-3	Value offered	Placebo/control	Method used to evaluate omega-3 intake	Method to evaluate the amount of omega-3 present in HM
Ribeiro et al[30]	Fish oil	0.72 g ω3/day	Primroseoil	24h reminder	Chromatography
Sherry et al[42]	Oil rich in DHA	Group 1: 200 mg DHA/day Group 2: 400 mg DHA/day	NI	Food survey and 3-day food records	Chromatography
Smit et al[37]	Oil rich in ARA and DHA	Group 1: 300 mg ARA/day Group 2: 300 mg ARA + 110 mg EPA and 400 mg DHA/day	No intervention	NI	Chromatography
Smithers et al[43]	Tuna oil	900 mg DHA +195 mg EPA + 54 mg ARA / day	Soybean oil	NI	Chromatography
Valentine et al[44]	Seaweed oil	1000 mg DHA	Soybean oil	3-day foodrecords	Chromatography
Weseler et al[45]	Milk drink made from powdered milk enriched with LCPUFAs	Group 1: 200 mg ARA/day Group 2: 400 mg ARA/day Group 3: 320 mg DHA + 80 mg EPA	Powdered milk	NI	Chromatography

Abbreviation: ALA, α − linolenic acid; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FOS, fructooligosaccharide; HM, human milk; LA, linoleic acid; LCPUFAs, long chain polyunsaturated fatty acids; NI, Not informed.
*DHASCO is an oil derived from a single-celled alga, mainly containing DHA, myristic, palmitic and oleic acids.

fatty acids in the form of linoleic acids (LAs) and α − linolenic acids (ALAs) are activated in the forms known as keto-acyl-CoA, and then used for the conversion of long chain polyunsaturated fatty acids and other polyunsaturated products, such as those derived from the series of desaturation and elongation reactions that are particularly active in the liver and, to a lesser extent, in other tissues.[8]

Linoleic and ALA fatty acids need to be ingested through food, since the human body does not have enzymes to synthesize them. Some vegetables synthesize them and are, therefore, an abundant source of these fatty acids, as well as the products derived from these vegetables. Omega-3 fatty acids (DHA and EPA) can be synthesized by the human body to a certain level, albeit a very limited one. The consumption of omega-3 sources through diet can be done by ingesting fish or fish oils, and foods enriched or fortified with these important fatty acids.[9]

Although ALA in humans is converted to EPA and DHA, the exact percentage of this conversion is unknown, but it is estimated to be low (5% EPA and 0.5% DHA).[10,11] Due to their enzymatic immaturity, children and especially neonates cannot convert all the DHA required for their development from ALA.[12] Therefore, feeding in the gestational period is of great importance as it determines the type of fatty acid that will accumulate in the fetal tissue. The essential fatty acids are transferred through the placenta, and in the third gestational trimester are deposited in the brain and retina of the fetus. It should be noted that the fetus withdraws a total of 50 to 75mg of polyunsaturated fatty acids from the mother, most of them being DHA.[13–16]

Numerous studies have been conducted to evaluate the effects of the supplementation of omega-3 and its metabolites in pregnancy and puerperium on the composition of HM. This is due to the synthesis of DHA probably occurring minimally in the mammary gland[6,17,18] as well as due to the role that this polyunsaturated fatty acid plays on visual acuity, cognition and in the formation of the nervous tissue of the newborn.[19]

Although supplementation appears to be the most reliable medium for increasing omega-3 levels in HM, there are numerous differences among the studies evaluated in relation to the following parameters: sample size, study design, timing of omega-3 supplementation (gestation and/or lactation), type of supplementation (fish oil, in natura fish consumption), and amount and type of omega-3 offered (EPA and/or DHA).

Regarding the diversity of the countries where the studies selected for this systematic review were performed, it is worth noting that the consumption of omega-3 rich foods in Western countries is well below that of other countries.[20] In the United States, the intake of omega-3 and its metabolites (DHA and EPA) was estimated at 1.6 and 0.1–0.2 g/day respectively, and the dietary ratio between omega-6 and omega-3 was $\approx$ 9.8:1.[21] A study with Canadian pregnant women showed that the average daily intake of omega-3 and DHA was 1.45 and 0.082 g/day respectively.[22] Populations living in coastal countries, such as Japan and Norway, where fish are widely consumed, have a higher dietary intake of omega-3 ($>$1 g/day), and consequently, high concentrations of DHA in their breast milk.[20,23,24] Although there is no official dietary recommendation for EPA and DHA in the US, several expert groups suggest a DHA intake of at least 200 mg/day, which may reach 1,000 mg DHA/day for pregnant and lactating women, and 1.4–2.7 g of omega-3, and suggest the omega-6/omega-3 ratio of $\approx$ 2–5:1.[21,25]

Corroborating the above recommendations, the consensus published by Koletzko et al[26] states that an average intake of at least 200 mg of DHA per day is advisable; it also states that consumption of up to 1 g of DHA or 2 to 7 g of omega-3 per day is safe. This amount can be achieved by consuming one to two servings of fish per week, including fatty fish such as herring, mackerel and salmon. However, it is known that the consumption of fish can contribute significantly to the exposure to contaminants such as methylmercury, which is particularly toxic to the developing brain and possibly harmful to infant growth. To decrease the amounts of methylmercury in the body, one should reduce the intake of contaminated foods during the pregestational and gestational periods. The fish with the highest levels of methylmercury are predatory fish such as marlin, pike, swordfish and shark. However, after an extensive literature review, the consensus points out that the beneficial effects of regular consumption of fish sources of DHA during pregnancy appear to overcome the potential drawbacks of the increased intake of contaminants.

Regarding the period of supplementation, the selected studies presented different time periods (pregnant and/or nursing) when omega-3 supplementation was performed and measured, which may partially justify the differences in the results we found. On this issue, in their randomized clinical trial, Boris et al[27] evaluated two hypotheses, namely: 1) whether omega-3 supplementation during pregnancy increased omega-3 levels at the beginning of breastfeeding; and 2) whether the continuation of supplementation after delivery was necessary to sustain the long-term increase in omega-3 levels. There was a marked drop in omega-3 levels in the group that stopped supplementation during the puerperium. Such a decrease in the concentration of DHA in breast milk as lactation progresses is corroborated by numerous studies.[4,28,29] On the other hand, the group that received fish oil during gestation and lactation showed levels of omega-3 three times higher, and double the levels of DHA.[27] It is worth mentioning that polyunsaturated fatty acids are deposited in the brain during the last gestational trimester, and that this process continues after delivery. Furthermore, the neurological development continues during the first years of life.[27] The results found by Ribeiro et al[30] also demonstrated that supplementation with fish oil limited to pregnancy was not as effective as supplementation during pregnancy and lactation. Therefore, supplementation during pregnancy and lactation is recommended by numerous studies.[20,30,31]

Important issues to take into account in these studies are the type of omega-3 source and the quantity that was supplied. It was observed that most of the selected studies used fish oil to increase the consumption of omega-3; however, some studies have used the supply of fresh food, fortified drinks and food education techniques. The use of fish oil has benefits, but it can lead to low compliance due to its adverse effects, such as fish flavor eructation, digestive discomfort and night sweats.[5,32] The randomized double blind clinical trial conducted by Dunstan et al[20] aimed to evaluate the effects of fish oil supplementation during pregnancy on the composition of HM and on the development of the infant in the first year of life. The concentration of fatty acids in the milk was analyzed on the third day, sixth week and sixth month after delivery. It was observed that women who received fish oil had a higher concentration of EPA and DHA in the milk on the third day and the sixth week after delivery.

Regarding the consumption of fish, the study by Henderson et al[33] demonstrated that ingesting 100–120 g of sardines 2 to 3 times a week resulted in increased levels of fatty acids without the need for fish oil. Harris et al[34] disagreed

Table 4 Controlled confounding factors, eligibility and exclusion criteria and main results found between supplementation of omega-3 sources on the fatty acid composition of human milk, 2000–2015

Authors	Estimator	Confounding factors controlled in the analysis	ligibility criteria	Exclusion criteria	Results
Atalah et al[5]	Median	Age, schooling, parity, initial weight, height, GA at baseline	GA < 14 weeks, age ≥18 years, primiparous, absence of chronic pathologies	NI	50% increase in omega-3 concentration in total fatty acids in HM, a non-statistically significant value ($p = 0.06$), probably due to the small sample size and insufficient adhesion level
Bergmann et al[38]	Average	Age, pregestational BMI, gestational weight gain, gestational age, parity type, parity, marital status, nationality, work, education, female gender, Apgar ≤ 7 in 10 minutes, umbilical cord pH ≤ 7.2, weight, length and head circumference	Pregnant, caucasian, healthy women, aged > 18 years and intending to breastfeed for at least 3 months	Severe illness, age < 18 years, non-Caucasian, increased risk of preterm or multiple pregnancy, allergy to cow milk protein, lactose intolerance, diabetes, smoking, alcohol consumption, participation in another study, consumption of other supplements, prematurity malformations, hospitalization > 1 week	The percentage of DHA in the breast milk was twice as high in the DHA-FOS group (0.50%) ($p < 0.001$), and the ratio of ARA to DHA in the DHA-FOS group compared with the other two groups was significantly reduced from 2.1 ± 0.76 to 1.0 ± 0.43 ($p < 0.001$). The Authors concluded that 200mg/day of DHA from mid-pregnancy to lactation appears to be adequate to improve the state of DHA in mothers and infants
Boris et al[27]	Average	NI	NI	NI	Comparing the two intervention groups, it was observed that women who received fish oil during gestation and lactation had increased levels of omega-3 compared with those who received until gestation only
Bortolozo et al[2]	Average	Age, schooling and income	Healthy, pregnant women aged 18–38 years, in the last trimester of pregnancy, non-smokers, no high-risk pregnancies, and adequate dietary patterns	NI	The milk of the mothers of the intervention group presented high levels of DHA and EPA at the 30th and 60th days, demonstrating that higher consumption of omega-3 could influence their concentration in HM, and there was no change between omega-3 and omega-6
Dunstan et al[20]	Correlation coefficient (R^2)	Parity, pre-gestational BMI, age and maternal allergy (allergic rhinitis or asthma)	Pregnant women between the 16th to the 20th gestational weeks and who had delivered after the 36th gestational week, with presence of allergic rhinitis, asthma or positive test in the Prick test	Pregnant smokers, with health problems and with fish consumption above two meals per week	In the intervention group, colostrum presented a high proportion of DHA and EPA when compared with the control group ($p < 0.001$). During the three moments, the drop was higher in the intervention group when compared with the control group ($p < 0.001$). However, the amount of DHA and EPA remained higher in the intervention group at 6 weeks postpartum when compared with the control group ($p< 0.001$). At 6 months, no differences were found between groups
Fidler et al[17]	Correlation coefficient (R^2)	Maternal age, height, weight (day 0), weight (day 14), BMI (day 14), milk secretion (mL/day), TL in HM (g/100 mL)	Healthy lactating mother, with omnivorous diet, with single, full-term, healthy newborns	NI	At baseline, there was no difference in fatty acid composition between the intervention and the placebo group. After two weeks of supplementation with 200mg of DHA/day, the milk from the intervention group contained a significantly higher percentage of DHA relative to milk from the placebo group ($p = 0.003$), a content almost 1.8 times higher of DHA. There was no significant difference in the content of any other fatty acids at any time point after supplementation.

(*Continues*)

Table 4 (*Continued*)

Authors	Estimator	Confounding factors controlled in the analysis	ligibility criteria	Exclusion criteria	Results
Francois et al[36]	Average	NI	Healthy women aged 28–39 years	NI	The omega-3 content in HM increased significantly over time, from 1.0% of total lipids (TL) at baseline to 6.8% of TL after one week of linseed oil supplementation. The omega-3 content remained high at 2 and 4 weeks. After 4 weeks of supplementation, the omega-3 concentration reached a peak of 7.7% of TL, and then returned to baseline (≈1.9% of TL) at 1 week after supplementation
Gaete and Atalah[1]	Median	Weight, height and BMI	GA > 37 weeks and exclusive breastfeeding	Women with diabetes, altered lipid metabolism and alcohol and drug dependence	After food education, the consumption of fish increased three times in relation to the initial consumption. The increased intake of DHA did not significantly modify the DHA content of the milk. However, in mothers with an intake of DHA > 200 mg/day there was a positive correlation between intake and milk content ($r = 0.71$, $p < 0.05$)
Gaete et al[31]	Median	Weight, height, BMI, parity, age of the newborn	GA > 37 weeks and exclusive breastfeeding	Women with diabetes, altered lipid metabolism and alcohol and drug dependence	After supplementation, an increase in the amount of EPA and DHA in HM was observed. DHA consumption in the intervention group increased significantly from 64 mg to 335.9 mg daily
van Goor et al[39]	Median	Maternal age, pregestational BMI, weight, gestational weight gain, GA at birth, birth weight and parity	Women with low risk, first or second pregnancy, and with single gestation	Vegetarian/vegan women and/or with diabetes mellitus	Compared with placebo, supplementation of ARA + DHA or DHA alone significantly increased the concentration of DHA in milk in both the second (59% and 43%, respectively) and in the 12th (56% and 52%, respectively) week after delivery
Hawkes et al[40]	Average	Maternal age, fish consumption, smoking, alcoholic beverages and side effects	Healthy women, age ≥18 years, single full-term infants, and breast-feeding for ≥ 12 weeks	Inflammatory diseases, use of anti-inflammatory drugs or fish oil supplements	The concentration of DHA in HM increased linearly in response to the diet with DHA. The authors concluded that the consumption of ≤ 600 mg/day of DHA and 140 mg/day of EPA for 4 weeks increased the concentrations of omega-3 and its metabolites in relevant tissues but did not cause changes in the concentrations of cytokines in human milk
Imhoff-Kunsch et al[13]	Correlation coefficient (R^2)	Age, GA, parity, BMI, schooling, GA at birth, prematurity and birth weight of the newborn	Women of gestational age between 18–22 weeks, who planned to breastfeed for at least 3 months, aged 18–35 years	High risk pregnancy, lipid absorption or metabolism disorder, regular intake of fish oil or supplements rich in DHA, and frequent use of certain medications	The concentration of DHA in breast milk in the intervention group was higher than for the placebo group ($p < 0.01$)
Jensen et al[18]	Correlation coefficient (R^2)	Age, parity, weight, height, GA, birth weight of the newborn	Pregnant women with the intention to exclusively breastfeed	Maternal age at birth < 19 or > 35 years, diabetes, egg allergy, gestational age < 37 weeks, and birth weight < 2,500 g or > 4,200 g	DHA supplementation increased plasma DHA concentrations in lactating women and in breast milk, resulting in a higher plasma concentration of DHA in children. A positive correlation was found between the DHA, EPA and ARA contents in maternal plasma and breast milk ($r^2 = 66.2\%$, $p < 0.001$)
Marc et al[32]	Average	Age, BMI, parity, schooling, work, marital status, use of vitamins, race and income	Childbirth with GA ≤29 weeks and intending to breastfeed	Age < 18 years or > 40 years, > 3 fish servings/week, use of omega-3 supplements, fish allergy, coagulation disorder, drug or alcohol use	The dietary DHA supplement provided during lactation increased the concentration of DHA in breast milk in mothers of preterm infants (GA ≤29 weeks) and in the plasma of these infants

Table 4 (*Continued*)

Authors	Estimator	Confounding factors controlled in the analysis	ligibility criteria	Exclusion criteria	Results
Olafsdottir et al[41]	Correlation coefficient (R^2)	Food intake, smoking, alcohol, drug use and schooling	Irish or having lived in the country for at least 15 years, single birth and breastfeeding	NI	EPA and DHA were significantly different between the groups, being 1.3–2.3 times higher in the milk of the intervention group when compared with the control group, without any negative effect on another fatty acids
Patin et al[35]	Correlation coefficient (R^2)	Age, BMI, Parity, gestational weight gain, weight and length of the newborn at birth	Exclusive breastfeeding, no smoking, no allergy/intolerance to sardines, birth weight $\geq$2500 g, GA between 37 and 42 weeks	NI	Consumption of 300 g of sardines per week increased DHA levels in HM
Ribeiro et al[30]	Averageand correlation coefficient (R^2)	NI	Age between 20–30 years, 30th week of gestation, no use of medication, no intolerance/allergy to fish, no use of dietary supplements with omega-3 and omega-6, and with intention to breastfeed exclusively	NI	The data confirmed that the omega-3 content in HM, DHA in particular, is influenced by the consumption of omega-3 by the pregnant woman. A positive correlation was found between omega-3 content in the phospholipids of erythrocytes of pregnant women and the content of these fatty acids in breast milk
Sherry et al[42]	Average	Age, BMI and skin color	Age $\geq$18 years, with full term infants, 4–6 weeks postpartum and who planned to breastfeed for $\geq$ 6 weeks	NI	Lactating women consumed $\sim$ 25% of the recommended amount of DHA/day. The data found demonstrated that supplementation significantly increased DHA in HM, as well as decreased the ratio of omega-6/omega-3
Smit et al[37]	Average	Maternal age, number of children and duration of lactation	Infants between the third and tenth months of breastfeeding	NI	The administration of 300 mg ARA + 110 mg EPA + 400 mg DHA increased the LCPUFAs content in HM, with no significant result
Smithers et al[43]	Average	Age, smoking, schooling, human milk production, breastfeeding at the end of the intervention, single gestation, gestational age at birth, gender and birth weight of the newborn	GA $<$ 33 weeks	Coagulation disorders, congenital or chromosomal anomalies, and multiple births in which not all live births were eligible	Mothers in the intervention group had 3-fold higher levels of DHA in HM compared with women in the placebo group but also had slightly lower linoleic acid content
Valentine et al[44]	Median	Age and stage of lactation	Donor to the human milk bank	Women who did not have enough milk to donate	The DHA content of the milk increased in the group supplemented with DHA capsules ($p < 0.05$)
Weseler et al[45]	Correlation coefficient (R^2)	Age, pregestational BMI, blood pressure, number of gestations, total fatty acids in milk and erythrocyte	GA (34–35 weeks), intention to breastfeed, pregestational BMI (18–27 kg/m^2), consumption of fish $<$ 2x per week, without use of omega-3 supplements, alcohol, cigarette, drugs or supplements	GA $<$ 37 or $>$ 43 weeks, allergy/intolerance to supplements and vegetarian components	It was observed that the concentrations of DHA in HM increased significantly after 2 weeks of supplement intake (320 mg DHA + 80 mg EPA)

Abbreviations: BMI, body mass index; ARA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GA, gestational age; HM, human milk; LCPUFAs, long chain polyunsaturated fatty acids; NI, not informed; TL, total lipids.

with this, and have observed that in order to increase 0.5 to 1 g of DHA in breast milk, it is necessary to consume 350–750 g of 1% fat or 75–150 g of 10% fish fat. In the study by Patin et al,[35] it was observed that the levels of DHA in HM increased with the ingestion of 300 g of sardines per week, with 5% fat, without the need to use fish oil supplementation. This study recommended the consumption of fish two to three times per week during gestation.

Gaete and Atalah[1] conducted a prospective study with 26 pregnant women, which consisted of an educational feeding strategy to recommend individual consumption of different preparations based on marine foods. A guide with information on the importance of maternal lactation to the newborn, and on the importance of fish consumption by the mother to increase DHA levels was also distributed. The strategy of food education is considered an important intervention to raise awareness about the need for fish consumption during the gestational and puerperal period.

The study by Atalah et al[5] aimed to evaluate the effects of the introduction of omega-3 fortified milk beverages (DHA and EPA) during gestation on the composition of HM and red blood cells. One-hundred and seventy-five women from the intervention group and 177 from the control group were evaluated in the clinical trial. The pregnant women were evaluated at three moments of the pregnancy and once after delivery to evaluate the consumption near the date of the interview. The evaluation of milk composition was performed in only 16 women, and a 50% increase in omega-3 in breast milk was observed. However, there was no statistical difference between the evaluated groups in relation to the amount of EPA and DHA, probably due to the small sample size.

Regarding the type of omega-3 offered, seven studies offered DHA and EPA, seven offered DHA only, and three offered DHA, arachidonic acid (ARA) and EPA. It was observed that the amount of DHA was always higher than that of EPA, probably because of its important role on the nervous system, cognition and vision. It is worth noting that there is no consensus regarding the optimal levels of DHA consumption at different stages of life. However, most technical groups recommend around 200 to 500 mg/day in the adult population, and, during gestation, it is recommended to consume fish between two to three times per week.[5]

There are numerous factors that contribute to the variability of EPA and DHA content in breast milk, such as lactation stage, gestational age, and maternal nutritional status. What is verified is that certain selected studies[20,27,30,36] did not control the analyses for important confounding factors, such as food consumption. Therefore, estimates of association may be compromised by the fact that certain studies did not quantify follow-up losses, but also because they did not control important confounding factors.

All selected articles showed the importance of supplementation of omega-3 in different forms (capsules, dairy drinks, strategy for feeding education, consumption of fish) on the nutritional composition of HM in the gestational and/or puerperal periods. However, four studies[1,5,27,37] did not reach statistical significance. This can be partially explained by the sample size, which can reduce the strength of the study to elucidate possible associations, possible adhesion reduction in relation to the intake of supplements and the food education practices employed, as well as the follow-up losses, which may cause a decrease in the validity of the results.

Conclusion

Although the studies were disparate in several methodological aspects, the importance of omega-3 supplementation in pregnancy and/or the puerperium, especially DHA, as well as the safety of its supplementation were observed with the data from the studies that composed this systematic review. However, it is of great importance that further studies be conducted to establish the adequate amount of omega-3s and their metabolites during gestation and lactation that will bring benefit to newborns.

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