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Lost In Translation: Bench to Bedside Evaluation of Omega-3 Dosing in Pregnancy on Child Neurodevelopment

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Abstract

Objective: To evaluate the variability in omega-3 supplementation dosing during pregnancy to support infant/child neurodevelopment in clinical trials compared to human equivalent dosages employed in animal studies. Additionally, to compare neurodevelopmental beneficial omega-3 supplement doses used in research studies to the omega-3 content of over the counter (OTC) and prescription prenatal supplements.

Study Methods: PubMed was used to identify clinical trials that evaluated the effect of omega-3 supplementation during pregnancy on neurodevelopment. Animal studies were selected if referenced in these clinical trials. Data compared: a) the number of clinical trials and animal studies with primary outcomes that were beneficial, indifferent, or harmful; and b) the human equivalent omega-3 doses used in animal studies versus clinical trials. Additionally, OTC and prescription prenatal supplements were evaluated for omega-3 content alongside the American College of Gynecology (ACOG) recommendation of 200 mg docosahexaenoic acid (DHA)/day during pregnancy. The cost for a 30-day supply of a supplement was compared based on the relative omega-3 content.

Result: Of 30 independent neurodevelopment outcomes identified in clinical trials, eight (26.7%) outcomes found benefit in omega-3 supplementation with the remainder showing no difference. No clinical trials reported harmful outcomes. All 16 animal studies demonstrated neurodevelopmental beneficial outcomes. The mean dose used in clinical trials was 844mg ±887mg while the mean human equivalent dose in animal studies was 10,996mg ±1164mg. Approximately, 31% of OTC and 59% of prescription prenatal products met or exceeded the ACOG recommendation of 200 mg DHA/day; however, neither had equivalent dosing used in supporting research studies. The cost of omega-3 content was significantly different for prescription, but not OTC, prenatal supplements.

Conclusion: Better collaboration between researchers and clinicians is needed in the design of animal and clinical studies to amend the current recommended omega-3 supplementation dosing during pregnancy and lactation to optimize child neurodevelopment.

Keywords: Neurodevelopment; Newborn; Obstetricians and gynecologists; DHA-deficient populations; Fetus; Child neurodevelopment; Omega-3 fatty acid; Animal studies; Hypothesized; Omega-3 dosing

Introduction

Neurodevelopmental benefits to the fetus and newborn, among other benefits, are often cited in omega-3 supplementation recommendations [1-5]. The American College of Obstetricians and Gynecologists (ACOG) guidelines recommend pregnant women to consume 200 mg/day of docosahexaenoic acid (DHA), the most beneficial component of omega-3 fatty acid [6-8]. Animal studies have suggested positive correlations between omega-3 supplementation in pregnancy and neurodevelopmental outcomes. However clinical trials investigating omega-3 supplementation in pregnancy on fetal and child neurodevelopment have demonstrated inconclusive evidence of benefit [9]. Interestingly despite the accepted and potential benefits of omega-3 supplementation, pregnant American women are among the most DHA-deficient populations in the developed world [10-12]. The primary objective of this quality improvement project was to address the hypothesis there has been a loss in the translation of omega-3 supplementation dosing used in research

animals to the omega-3 supplementation dosing used in clinical trials and ultimately implemented in clinical practice. This was derived on the observation that there have been substantially lower doses of omega-3 used in clinical trials as compared to animal studies, which may contribute to the lack of consistent neurodevelopmental benefits observed in clinical trials. Another concern observed was there was a disconnection between clinical trial omega-3 supplementation dosing and translation to current clinical practice omega-3 supplement dose recommendations. Hence, the second objective was to assess the omega-3 content of common over the counter (OTC) and prescription prenatal products to compare ACOG recommendations and omega-3 dosing in research studies. Finally, it was hypothesized that perhaps cost was a driver behind clinical practice omega-3 dosing recommendations so the 30-day cost of supplements relative to their omega-3 content was evaluated.

Methods

This quality improvement study was approved and reviewed by the University of Texas Health Sciences Center (UTHealth) Institutional Review Board (IRB) as quality improvement research. In this quality improvement study the national library PubMed database was employed to identify peer-reviewed, published randomized, controlled clinical trials (RCTs) with search terms that included: "omega-3 and pregnancy" and a pre-designated search term including neurodevelopment, cognition, intelligence, IQ, memory, visual acuity, and attention. Animal studies were selected if included as a cited reference in the rationale for the clinical trials that met inclusion criteria for the current study. Clinical trials with sample size fewer than 20 subjects or that were not randomized control trials were excluded. If the research publications were not available in English language, inaccessible/ not cited through PubMed, or if unable to determine omega-3 dosing then both clinical trials and respective animal studies were excluded. Clinical trials and animal studies were analyzed using their primary neurodevelopmental outcomes, which could include those outcomes delineated by the search terms (i.e., memory, attention, etc.), as well as other features of infant and child neurodevelopment (i.e., language, behavior, etc.). The primary outcomes from each study were identified using the authors' primary question or objective. Secondary outcomes were not considered when not powered appropriately based on study design. If a clinical trial or animal study sought to assess a single neurodevelopmental feature at two distinct time points as stated in the primary question, each time point was considered as a separate primary outcome of the same study and was counted individually. Additionally, follow-up trials were excluded from the total mean dose calculation of all clinical trials. This was to ensure that the data was not skewed to overrepresent clinical trials with multiple follow-up publications that studied one sample population. Follow-up trials were instead included in the evaluation as additional primary outcomes of the original RCT rather than as unique studies. The primary outcomes from the clinical trials and animal studies were sorted in one of three categories: beneficial, indifferent, or harmful based on the study conclusion for omega-3 supplementation to support the respective neurodevelopmental outcome.

The number of primary outcomes in each of these categories as well as the mean human equivalent omega-3 doses used in animal studies versus clinical trials were summarized. For the secondary objective of this evaluation, OTC and prescription prenatal supplements were identified and evaluated for omega-3 supplementation dosage using major retailers' websites, GoodRx.com, and Lexicomp [13-14]. Supplements were included if they were marketed as prenatal supplements. Supplements were excluded if they were not marketed for pregnant mothers, supplement information could not be found, it appeared that the product had been discontinued, or the product was marketed for a single ingredient (i.e., folic acid, prenatal probiotic, etc.) For OTC prenatal supplements, all omega-3 content information was obtained from the product's nutrition information on respective product's website, or from product image on retailer's website if unclear from product-specific website. For prescription products, supplement information was obtained using drugs.com, DailyMed-NIH, and products' websites [15]. The total omega-3 and specific DHA content of each product was evaluated alongside the ACOG DHA recommendation of 200 mg per day during pregnancy. Other data was also collected using the supplement information, such as eicosapentaenoic acid (EPA) content, whether the DHA was derived from plant or animal products, and the packaging forms within which the omega-3 was sold (i.e., multivitamin, multivitamin + soft gel, soft gel alone.) Finally, the cost for a 30-day supply of a supplement was recorded relative to the number of daily servings of omega-3 contained within each product. For OTC prenatal supplements, product prices were first sought out on the supplement brand's website if a website existed. If a product's brand recommended purchasing through a specific retailer, this price was used to calculate the cost of a 30-day supply. If a product website could not be found for a supplement, or the supplement brand's website did not list a price, a supplement's price was noted from one of several vitamin retailers. The average wholesale price for prescription drugs was identified using Lexicomp Online [16].

All information was entered into a database by one investigator. Clinical trial and animal study data was independently verified by two other investigators, while prescription and OTC data was also verified by a licensed pharmacist. Statistical comparisons were completed by employing paired-T-tests.

Result

A total of 40 clinical trials and follow-up studies were identified in the literature search. Eighteen publications were excluded because they did not meet study inclusion criteria, leaving a total of 22 clinical trials and follow-up studies to be included for analysis with a total of 16 referenced animal studies identified. After grouping clinical trials with their follow-up trials, 13 unique clinical trials were identified. There were 30 independent neurodevelopment outcomes identified in the

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clinical trials, with eight (26.7%) of these outcomes finding a benefit in omega-3 supplementation and the remainder showing no difference in outcomes with supplementation; no trials reported any harmful outcomes. In the animal studies, all 16 independent neurodevelopmental outcomes demonstrated benefit with omega-3 supplementation. The mean dose used in neurodevelopment-focused clinical trials was 844 ±887 mg, which was 7.7% of the mean human equivalent dose used in animal studies (10,996 ±1164 mg) (Table 1,2). Of the 13 unique clinical trials, eight trials (61.5%) found that at least one of the primary outcomes was benefitted with omega-3 supplementation while five clinical trials (38.5%) found no difference in any primary outcome with the use of omega-3 supplementation. The mean dose used in the eight clinical trials that found at least one primary outcome benefit of omega-3 supplementation was 950 ±1108mg, with doses ranging from 214 to 3300mg. The mean dose used in the five trials that found no difference in outcomes with omega-3 supplementation was 674 ±390mg, with doses ranging from 220 to 1200 mg. Of the 148 OTC prenatal supplement products identified, 134 met the inclusion criteria, while 89 of the 108 prescription prenatal supplement products identified met the inclusion criteria. 41 of the 133 OTC products (30.8%) and 51 of the 86 prescription products (59.3%) for which DHA content could be determined met or exceeded the ACOG recommendation of 200 mg DHA per day (Figure 1,2). Sixty-two of the 134 OTC products (46.3%) included and 56 of the total 89 prescription supplements (62.9%) included contained any amount of omega-3. Of note, more than half of all prenatal supplements that contained omega-3 included the omega-3 as DHA within the multivitamin tablet, which has less bioavailability in this form. Among the 133 OTC products for which pricing information was readily available, there was no difference ($p>0.05$) in cost based on omega-3 content. The cost of a 30-day supply of OTC supplementation averaged $22.85 ±14.33, and prices ranged from $1.15 to $85.90. Among 31 prescription prenatal products with pricing information available on Lexicomp, there was a statistically significant increase in average wholesale price with increasing omega-3 content ($p<0.01$). The average price for a 30-day supply of prescription supplement was $131.66 ±83.71, and prices ranged from $20.40 to $276.00 (Figure 3).

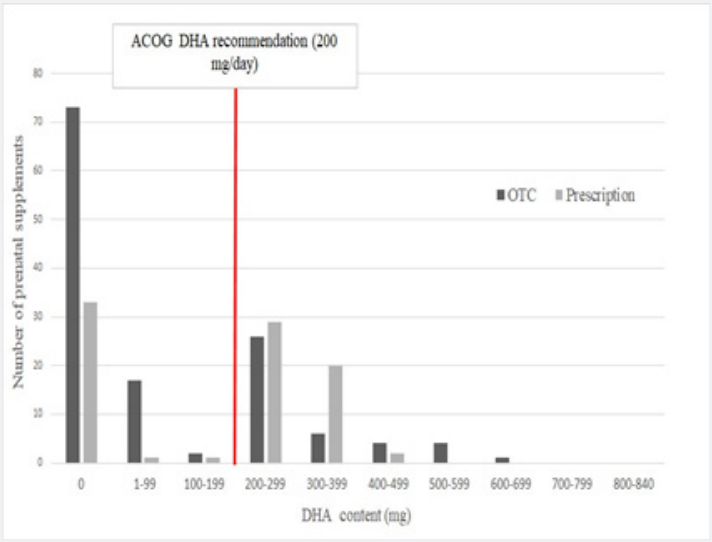

Figure 1: Number of OTC and prescription prenatal products by DHA content.

Table 1: Clinical trials versus animal studies omega-3 dosage and primary neurodevelopmental outcomes data.

Sample	Total number	Mean dose or human equivalent dose (mg) ± SD*	Range of doses (mg)	Total primary outcomes	Beneficial Outcomes by omega 3	Outcomes unaffected by omega 3	Harmful Outcomes by omega 3
All clinical trials 18-39	13	844 ±887	214-3300	30	8	22	0
All animal studies 40-55	16	10996 ±11645	134-42,000	16	16	0	0

*Standard deviation

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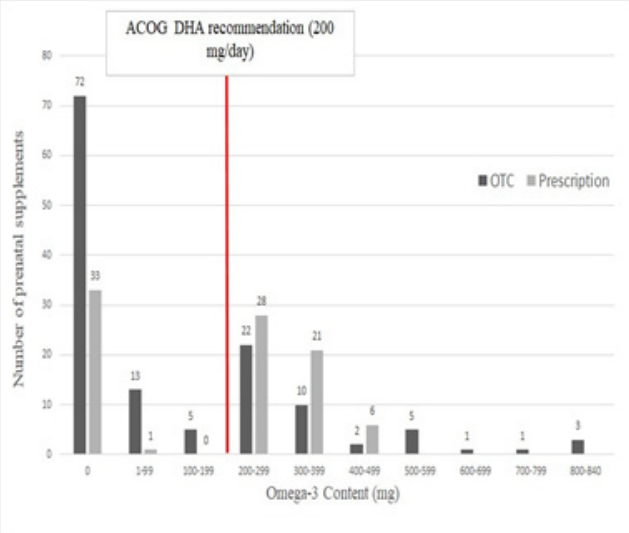

Figure 2: Number of OTC and prescription prenatal products by DHA content.

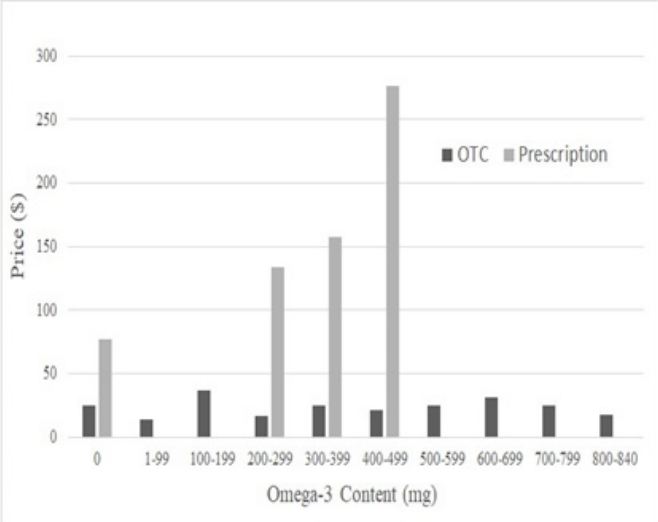

Figure 3: Average retail price (OTC) or average wholesale price (prescription) for a 30-day supply of prenatal supplements relative to omega-3 content.

Table 2: OTC* versus prescription supplement information regarding omega-3 content, pricing, and packaging.

Supplement information	OTC* omega-3 supplements	Prescription omega-3 supplements
Mean total omega-3 content of supplements containing omega-3 (mean±SD†, range)	276±205 (0-840)	282±82 (0-500)
Mean DHA‡/EPA§ ratio‖	6:01	25:01:00
Omega-3 products derived from fish oil (% of total omega-3containing products)	35 (56.5)	25 (44.64)
Number of DHA‡-containing multivitamins (% of total omega-3-containing products)	34 (54.8)	37 (66.1)
Number of multivitamins + DHA‡ soft gel combination packs (% of total omega-3containing products)	9 (14.5)	19 (33.9)
Mean price ($) for 30-day supply (mean±SD†, range)	22.85±14.33, (1.15-85.90)	131.66±83.71 (20.40-276.00)

*Over the counter
†Standard deviation
‡Docosahexaenoic acid
§Eicosapentaenoic acid
‖EPA content found for 55 OTC and 52 prescription products containing omega 3.

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Discussion

This evaluation of clinical use of omega-3 supplementation has taken a different approach and aimed to understand why current literature is inconclusive and the recommended use of omega-3 supplementation in clinical practice is ambivalent. Rather than conducting a literature review that synthesizes conclusions drawn from various studies, this was a close evaluation between clinical study dosing, primary outcomes, and correlative animal studies. The findings illustrated the discrepancies found between the omega-3 supplementation dosing used in clinical trials and omega-3 supplementation dosing used in animal studies referenced in the rationale for these clinical trials, demonstrating that omega-3 supplementation dosing benefits have been lost in translation from bench to bedside. Even the implementation of clinical trial omega-3 supplementation dosing into clinical practice has been lost in translation. Understanding these discrepancies on dosing of omega-3 supplementation during pregnancy may provide an opportunity to re-address current clinical recommendations for omega-3 supplementation during pregnancy. Of note, the ACOG recommendation for omega-3 supplementation during pregnancy is 200 mg DHA per day. In contrast, the mean dose of omega-3 supplementation for our included clinical trials that found a benefit to supplementation was 950 ±1108mg, with doses ranging from 214 to 3300mg. Hence, the ACOG recommendation is significantly lower than the mean dose used in clinical trials. Moreover, it is concerning that around 70% of OTC and 40% of prescription prenatal products fail to even meet or exceed ACOG's current omega-3 supplementation recommendation.

This quality improvement study demonstrated there is an insufficiency of omega-3 content in majority of the prescription and all the OTC prenatal products compared to the actual beneficial omega-3 supplementation dosing used in clinical trials. This will hopefully in turn encourage clinicians to guide patients towards appropriate products for omega-3 supplementation. For example, consider a separate omega-3 soft gel supplement that provides 800 to 1000 mg of DHA during pregnancy in addition to a daily prenatal multivitamin. Additionally, current literate states fish oil is a better source of omega-3 as opposed to plant sources because the human body physiologically can metabolize and utilized DHA from animal verses plant sources. Many prenatal supplements on the market do not use fish-oil derived omega-3, which may influence the efficacy of a supplement and should be considered when recommending specific supplements [17]. While not directly evaluated in this study, the duration of omega-3 supplementation initiated during pregnancy should be extended throughout breastfeeding since neurodevelopment continues well into first year of life. The major strength of this report is the focus on identifying differences in dosing between animal studies and clinical trials that may account for the inconclusive literature about omega-3 supplementation in clinical trials. This study also emphasized the importance of understanding the content and cost of the omega-3 supplementation in prenatal products, many of which are not even compliant with current ACOG recommendations. Limitations of this analysis arose from the inability to access published studies' raw data, which may have provided more insights into study compliance rates and rationale behind selecting investigational doses in clinical trials as well as animal studies. Future studies should consider using multiple experimental doses that are within range of equivalent dosing as well as the duration of omega-3 supplementation used in animal studies that have demonstrated benefit in supporting in utero/infant/child neurodevelopment. This will help to identify an optimal omega-3 supplementation dose that provides benefits during pregnancy and lactation. Pre-clinical researchers need to remain cognizant of the utility of methodology and conclusions that will be translated to bedside practice. Animal studies often use doses so high as to be infeasible for clinical trials and clinical practice either due to human equivalent doses that would require multiple pills per dose and/or would be associated with excessively high costs. Additional studies are needed that keep such limitations in mind. In conclusion, better collaboration between pre-clinical and clinical researchers is needed in the design of animal and clinical studies to refine omega-3 supplementation dosing and duration of supplementation during pregnancy and lactation to optimize child neurodevelopment. Clinicians in practice need to be aware of the inadequate content with higher cost of omega-3 supplementation in prenatal products, which are not even compliant with current ACOG recommendations, to guide patients towards more appropriate OTC, single-ingredient omega-3 supplementation products to use during pregnancy to support fetal and ultimately optimize child neurodevelopment.

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