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Can dietary omega-3 fatty acid supplementation reduce inflammation in obese pregnant women?

A Discussion paper of a Randomized Double-Blind Controlled Clinical Trial by Haghiac M, et al., in PLoS One 2015; 10(9): p. e0137309

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Abstract

Omega-3 fatty acids are well known for their anti-inflammatory actions in humans. In this article a study that aimed to investigate the effects of omega-3 supplementation on the inflammatory response of overweight/obese pregnant women, is discussed. The study was a randomized, double-blind controlled trial conducted in overweight/obese pregnant women that were randomly assigned to receive DHA plus EPA (2 g/day) or the equivalent of a placebo. Analysis revealed that in the intervention group subjects had lower levels of CRP plasma concentrations, whereas no significant changes were observed in other inflammatory markers' levels. These findings suggest that omega 3 supplementation for >25 weeks reduced inflammation in maternal adipose and the placental tissue, with TLR4 appearing to be a central target of the anti-inflammatory effects at the cellular level. In conclusion, omega 3 supplementation during pregnancy is a potentially essential intervention in order to reduce maternal and fetal risk due to inflammatory response.

Key words: omega-3 fatty acids; inflammation; obesity; pregnancy

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Introduction

Pregnancy is normally accompanied by a state of subclinical inflammation which has an essential role on establishing and maintaining a viable pregnancy, by ensuring the proper host defense against any possible invading pathogens [2-6].Intrauterine bacterial or viral infections are responsible for various severe complications such as abortion, preterm labor, preeclampsia and intrauterine growth retardation (IUGR) and this is the reason why low-grade inflammation is vital for a healthy pregnancy [3]. Pregnant women, compared to their non-pregnant counterparts, exhibit leukocytosis, increased complement activation and alterations in peripheral blood leukocyte populations [4]. Moreover, studies have demonstrated that trophoblasts express a specific category of receptors named Toll-Like Receptors (TLRs), known for their role on inflammatory cascades in human body and these findings suggest the potential role of TLRs signaling in the placenta during pregnancy [3]. The expression and activation of these receptors is finely regulated during each trimester of pregnancy, leading to the conclusion that inflammatory process needs to be modulated and specifically regulated during each phase of pregnancy in order to exert a beneficial role [3, 4]. However, abnormal, premature or dysregulated maternal inflammatory response has been linked with adverse outcomes, such as poor perinatal and placental development, preeclampsia, pre-term labour and fetal growth restriction, highlighting the importance of strict regulation of the inflammation degree throughout pregnancy [4]. Altered utero-placental perfusion and inflammation-induced alterations in maternal hemostasis, local vasoconstriction and/or oxidative/nitrosative stress, are some potential mechanisms linked to the pathogenesis of negative pregnancy outcomes caused by aberrant maternal inflammation [4].

Obesity is associated with a chronic low grade inflammation and insulin resistance in humans. Normal pregnancy is characterized by a state of insulin resistance, with a 50% reduction in insulin-mediated glucose clearance, and a ~250% increase in insulin production to maintain maternal euglycemia. Obese pregnant women, in particular, have greater risk to develop insulin resistance and adipose tissue inflammation in comparison to normal weight women [5]. They moreover have greater risk for maternal and fetal morbidity and mortality as well as pregnancy complications such as preeclampsia, compared with their normal weight counterparts [4, 5].

Pregnant women benefit from increased fish consumption, which is rich in omega 3 fatty acids (FA), EPA and DHA. In animal models, EPA and DHA improve insulin sensitivity whereas in human models omega 3 fatty acids supplementation potentially decreases the risk for type 2 diabetes mellitus development and reduces insulin resistance [1]. Omega 3 fatty acids are also potential anti-inflammatory agents in humans. These fatty acids are able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and leukocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, production of inflammatory cytokines, and T-helper 1 lymphocyte reactivity. In addition, EPA leads to the production of eicosanoids that often have lower biological potency than those produced from arachidonic acid. EPA and DHA mediate the secretion of anti-inflammatory and inflammation resolving mediators called resolvins, protectins and maresins [7]. Mechanisms underlying the anti-inflammatory actions of marine omega-3 fatty acids include altered cell membrane ph ospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B (NFkB) so reducing expression of inflammatory genes and also activation of the anti-inflammatory transcription factor peroxisome proliferator activated receptor γ (PPARγ) [7]. The anti-inflammatory effects of omega-3 polyunsaturated fatty acids *via* the aforementioned mechanisms suggest that they may be useful as therapeutic agents in disorders with an inflammatory component [8, 9].

Thus, in the present discussion paper we comment on the findings of a randomized double-blind controlled clinical trial that was aimed to investigate

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the anti-inflammatory actions of omega 3 fatty acids dietary supplementation in the placenta, maternal blood and adipose tissue of overweight and obese pregnant women, and also identify the underlying cellular mechanisms [1].

Dietary omega-3 fatty acid supplementation reduces inflammation in obese pregnant women: A randomized double-blind controlled clinical trial [1]

The study is a double-blind controlled clinical trial conducted in a sample of pregnant women who were asked to receive oral supplement containing 800 mg docosahexaenoic acid (DHA, 22: 6 n^{-3}) and 1200 mg of eicosapentaenoic acid (EPA, 20: 5 n^{-3}). The daily dosage was 4 capsules, or matching placebo capsules, divided into 2 capsules twice a day beginning from enrollment and until delivery. The study was approved by the Institutional Review Board of Metro Health Medical Center/Case Western Reserve University. Prior to participation, all subjects signed a written informed consent form. Concerning the sample, 120 pregnant women were initially recruited, but 100 individuals were the final participants (16.7% dropout rate, 50 women in the placebo and 50 in the supplementation group). The sample size was determined after assuming a power of 80% and with a $p = 0.05$ in order to detect a 1.5-fold decrease in inflammatory markers after taking the omega 3 supplements compared to placebo. The sample was collected between September 2009 and August 2011, at Metro Health Medical Center in Ohio, United States of America. Eligibility criteria for enrollment were a confirmed singleton pregnancy and Body Mass Index (BMI weight/height2) >25 at the first antenatal visit, gestational age between 8 weeks and 16 weeks based on clinical and ultrasound prior to 20 weeks gestation. Moreover, all subjects (other than BMI >25 kg/m^2) had to be generally healthy.

The study's participants were randomly allocated into the two groups using a computer generated randomization table. Randomization and treatment assignment were carried out by the research coordinators. It is a double-blind trial so study group assignment was not known by study participants, neither their health care providers, nor the research staff. However, authors do not mention any additional details concerning restrictions during randomization or any methods used to implement the random allocation sequence, clarifying whether the sequence was concealed until interventions were assigned. Authors do not also mention how the success of blinding was evaluated. Blister packs supply took place on a monthly basis during routine obstetrical visits at what time compliance and side effects were assessed for each participant. There were two visits in the clinical research unit (CRU) at Metro Health Medical Center for each participant, first between 8–16 weeks and second between 34-36 weeks. In each visit, researchers obtained information on height and weight, as well as a sample of maternal blood for plasma cytokine measurements, fasting glucose and insulin measurements. Anthropometric measurements of participants at visit 1 are demonstrated in **Table 1**, whereas data for visit 2 are not mentioned by the authors. Further data on the methods used for weight and height measurement or other anthropometric measurements are not mentioned by the authors. Food frequency questionnaires were used to collect data on dietary habits. Since they have been partially analyzed, the authors have chosen not to use incomplete information, thus further details about supplement use (vitamins, calcium, iron etc) are not available. Placenta tissue and cord blood were obtained immediately after double-clamping of the umbilical cord.

Regarding statistical analysis of the data, they were analyzed according to the intention-to-treat principle. The changes over time were analyzed as the differences in measurements at visit 2 minus visit 1 and compared between groups using Student t-test. Significance was set at $p<0.05$. Authors did not mention specific objectives and hypotheses of the study and did not clearly define any methods used to enhance the quality of measurements.

In total, 620 women were screened and 156 agreed to be enrolled in the one week run-in. In order to successfully complete the run-in the subjects had to take at least 50% of the placebo capsules verified by pill pack count. 84 women failed the run in. Of

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Table 1. **Anthropometric characteristics of the clinical trial participants at visit 1 (baseline), as reported by Haghiac M et al. [1]**

Subjects	Placebo group (n = 24)	ω-3 treated group (n=25)	p-value
Maternal age (years)	27 ± 5	27 ± 5	0.9
GA at randomization (weeks)	14.2 ± 2	14.3 ± 2	0.2
Body Mass Index (kg/m2)	32 ± 6	33 ± 6	0.3
Weight (kg)	80 ± 11	90 ± 20	0.03
Weight gain (kg)	8.8 ± 5.1	9.7 ± 6.5	0.6
Ethnicity (AA/Cauc/other)	6/11/7	11/10/4	0.3
Parity (0/ ≥1)	5/19	7/18	0.5

Data are means ±SD. p-value: comparison between visits within each group. Maternal blood was obtained following fasting. GA-Gestational age; AA-African American; Cauc-Caucasian; other-Hispanic, Asian.

those who completed the run-in, 36 were randomly assigned to the ω-3 FA supplement group and 36 to the placebo group. In the placebo group, 11 were lost to follow up (7 missed visit 2, 1 spontaneous abortion, 2 unable to contact, 1 moved away) and 24 subjects completed the study. In the ω-3 FA group 10 subjects were lost to follow-up (7 missed visit 2, 1 spontaneous abortion, 1 unable to contact, 1 moved away) and 25 subjects completed the study.

Referring to the baseline characteristics of the subjects (**Table 1**), maternal age was in average 27 years old in both groups. The mean gestational age was 14.2 weeks in the placebo group and 14.3 weeks in the intervention group. Subjects in the placebo group were mostly Caucasian whereas in the intervention group mostly African American. The only statistically significant difference between the two groups was the weight at randomization, with subjects in the placebo group having an average 80 kg whereas subjects in the intervention group having an average 90 kg. HOMA-IR Index equally changed in both groups, indicating that maternal insulin resistance was not modified by omega 3 supplementation. The metabolic parameters at baseline and after the intervention are presented in **Table 2** as they appeared in the original paper, along with the differences between the two groups. A significant decrease was observed in maternal plasma CRP levels in the intervention group vs. placebo group ($p< 0.05$). There was less of an increase in plasma interleukin 6, but no significant difference in plasma interleukin 8, adiponectin and leptin concentrations between the two groups. The subjects supplemented with ω-3 FA had significantly lower expression of IL6, IL8, TNFα and TLR4 mRNA (p<0,001) in adipose and placental tissue compared with the placebo group.

In an attempt to elucidate the exact anti-inflammatory mechanisms of omega-3 FA, in vitro experiments were conducted in cells isolated from maternal subcutaneous adipose tissue and placenta. These cells were changed to fresh medium after overnight plating followed by incubation under serum-free culture conditions for 24 hours in the presence or absence of fatty acids. Trophoblast and adipose cells were cultured in the presence of palmitate (PA) and oleate (OA) the two fatty acids most abundant in human adipose tissue. Lipopolysaccharide (LPS), which is the natural TLR4 ligand was used as a positive control in both cell types. It needs to be mentioned that PA is the most abundant saturated fatty acid constituent of human adipose tissue triglycerides and there is a progressive increase in the proportion of PA in maternal blood from first to third trimester [1]. Similarly to LPS, PA activates a TLR4-induced inflammatory cascade

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Table 2. **Metabolic parameters of the participants of the clinical trial at Visit 1 and Visit 2 as reported by Haghiac M et al., [1].**

Subjects	Placebo group (n = 24)			ω-3 treated group (n=25)			p-value		
	Visit1	Visit2	Δ(V2-V1)	Visit1	Visit2	Δ(V2-V1)	Visit1	Visit2	Δ(V2-V1)
CRP (μg/ml)	12.8 ± 9.7	13.6 ± 7.8	0.8 ± 6.9	13.6 ± 11.6	10.4 ± 8.2	-3.2 ± 5.2	0.8	0.2	0.05
Glucose (mg/ml)	80 ± 7	77 ± 6	-3 ± 7	80 ± 6	82 ± 9	2 ± 10	0.9	0.03	0.04
Insulin (μU/ml)	6.6 ± 3.0	9.2 ± 5.0	2.6 ± 5.6	9.8 ± 6.7	12.5 ± 6.2	2.7 ± 6	0.06	0.05	0.9
Interleukin 6 (pg/ml)	1.9 ± 1.5	2.4 ± 1.2	0.5 ± 1.4	2.1 ± 1.5	2.3 ± 1.2	0.1 ± 1.1	0.7	0.6	0.3
Interleukin 8 (pg/ml)	2.9 ± 1.2	3.5 ± 1.5	0.5 ± 1.7	3.7 ± 1.5	4.5 ± 1.7	0.6 ± 0.7	0.03	0.02	0.8
Adiponectin (μg/ml)	11.7 ± 4.4	9.4 ± 4.4	-2.3 ± 3.7	11.3 ± 4.6	9.7 ± 4.4	-1.9 ± 4.5	0.7	0.8	0.7
Leptin (ng/ml)	50 ± 27	54 ± 25	4 ± 20	48 ± 27	58 ± 31	12 ± 23	0.8	0.7	0.3

Data are means ± SD. p-value – comparison between placebo and ω-3 treated groups at visit 1, visit 2 and Δ(V2-V1) = Visit2-Visit1. Maternal blood was obtained following fasting

in trophoblast and adipose cells in human. In the present experiment, PA treated trophoblast cells exhibited an increase in TLR4, IL6 and IL8 mRNA expression. PA-stimulated cells showed a 5.3-, 8.3- and 10-fold increase (p<0.0001) in TLR4, IL6 and IL8 gene expression respectively, when compared to control untreated cells, which highlights the pro-inflammatory effect of palmitate in human body. EPA and DHA when added to the maternal subcutaneous adipocytes and placenta cells culture medium together with PA, they significantly decreased its inflammatory effect, as described above, by 66 and 70%, respectively. The anti-inflammatory effects of EPA and DHA were also analyzed in adipose cells. PA induced a 4 to 30 fold increase in TLR4, IL6 and IL8. Addition of DHA and EPA together with PA decreased the cytokine expression in adipose cells by 61 to 68% for IL8 and by 76 to 80% for IL6. The same inhibitory trend was observed when EPA and DHA were added 2h prior to PA treatment. Moreover, a decreased expression of TLR4 in trophoblasts in the presence of EPA or DHA was observed. These data suggest that addition of DHA or EPA to the culture medium prevented the PA induced-TLR4 and inflammatory cytokines in both adipose and trophoblast cells, rather than directly lowering cytokine expression. No adverse events or any side effects were mentioned.

Discussion of the effects of dietary omega-3 fatty acid supplementation on inflammation in obese pregnant women

The main finding of the study was that omega 3 supplementation reduces inflammation in overweight/obese pregnant women. Receiving supplements for 25 weeks resulted in lower maternal CRP levels and lower expression of inflammatory genes in the adipose tissue and the placenta. The duration of the clinical trial was possibly short enough to allow researchers to detect significant changes in other markers' concentrations.

Regular consumption of ω-3 PUFAs, mainly EPA

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and DHA, has been associated to the prevention and palliation of chronic inflammation [10]. The anti-inflammatory properties of omega-3 fatty acids are based on their ability to decrease the production of pro-inflammatory cytokines by several tissues and cells. Omega-3 FAs are substrates for the synthesis of eicosanoids. Oxygenated lipid mediators of these fatty acids that are produced through specific metabolic pathways tend to act as anti-inflammatory agents [7, 10-12]. Marine oil supplements potentially suppress inflammation, by decreasing the production of TNFα, well known as pro-inflammatory agent [10, 11]. Fish oil supplementation is also associated to lower ω-6/ω-3 index in plasma and membranes, which means lower inflammatory load [10]. Moreover, omega-3 PUFA originating from fish oil activate PPAR-γ in adipose tissue, increasing the expression, secretion and plasma levels of the anti-inflammatory hormone adiponectin [7, 11, 13]. Lastly, omega-3 FAs decrease plasma triglyceride concentration, which is a causal cardiovascular risk factor, possibly through promotion of inflammation. Thus, omega-3 supplementation could be considered to have anti-inflammatory properties, through the aforementioned mechanisms [14]. It needs to be mentioned that besides their anti-inflammatory actions, omega-3 fatty acids are essential for proper fetal growth and in particular for the development of the brain and retina [9].

During pregnancy inflammation levels are naturally increased, as well as oxidative stress, reflected by increases in various acute phase reacants and cytokins, mainly oxidized lipids, interleukin-6 and prostaglandins [2, 6, 15, 16]. This is happening in order to provide protection from any possible invading organism and ensure the maintenance of a healthy pregnancy [3, 4, 17]. Excessively high levels of inflammation are associated with adverse birth outcomes, such as low birth weight, spontaneous preterm delivery, intrauterine growth restriction or preeclampsia [2, 15, 16, 18]. Increased inflammation during pregnancy is also associated with gestational diabetes and metabolic diseases of the offspring later during adulthood including obesity, dyslipidemia, type 2 diabetes mellitus, and hypertension, whereas the risk is greater when maternal excessive body weight coexists [5, 15, 19, 20]. Obese pregnant women are particularly at increased risk for the adverse outcomes mentioned above, because according to recent data chronic or dysregulated inflammation usually coexisting with excess adiposity is a major contributor to these complications [5, 15, 16, 21]. Obese pregnant women have increased levels of proinflammatory cytokines in maternal circulation and placental tissues, and increased activation of placental inflammatory pathways compared to normal weight pregnant women [21].

As already mentioned, obesity is a condition usually accompanied by low-grade chronic inflammation and increased oxidative stress, which subsequently affect other tissues, obstruct insulin signaling and β-cells function, contributing to the development of endothelial dysfunction and various metabolic disorders such as type II diabetes mellitus [10, 22, 23]. Increased adipose tissue mass is generally associated with activation of inflammatory pathways [16]. In particular, visceral fat compared to subcutaneous fat, is characterized by higher secretion of pro-inflammatory cytokines such as TNF-α and IL-6, and lower secretion of adiponectin [22, 23]. Besides adipocytes, adipose tissue contains macrophages and other immune cells who locally produce chemoattractants and whose number is excessively increased in obesity, contributing to adipose tissue inflammation. The recruitment of these cells combined with the increased production and secretion of pro-inflammatory cytokines and biomarkers by adipocytes are some of the major mechanisms linking obesity to low-grade chronic inflammation [22].

Conclusion

In conclusion, pregnancy is an event characterized by subclinical maternal inflammatory response, which is responsible for the protection against invading pathogens and the maintenance of a viable fetus. The effective regulation of inflammation degree is a major part of a healthy pregnancy, as increased inflammatory levels are associated with severe complications. Overweight and obese

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women develop abnormal inflammatory response and thus they are in greater risk for adverse pregnancy outcomes. Omega 3 fatty acids have known anti-inflammatory properties in human body, thus supplementation of these fatty acids could potentially modulate excessive inflammation during pregnancy. However, more studies need to be conducted in order to elucidate the role of omega-3 supplementation in pregnant women, the underlying mechanisms and the overall benefit gained from such an intervention.

Conflict of Interest

All authors declare no conflict of interest.

Περίληψη

Μπορεί η συμπληρωματική χορήγηση Ω-3 λιπαρών οξέων να συμβάλει στη μείωση της φλεγμονής σε παχύσαρκες εγκύους;

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Η α ωμέγα 3 πολυακόρεστα λιπαρά οξέα είναι γνωστά για τις αντιφλεγμονώδεις ιδιότητές τους στον ανθρώπινο οργανισμό. Στην παρούσα εργασία γίνεται συζήτηση σχετικά με μια μελέτη που διερεύνησε την επίδραση των συγκεκριμένων λιπαρών οξέων στη φλεγμονώδη απόκριση υπέρβαρων και παχύσαρκων εγκύων γυναικών. Πρόκειται για μια τυχαιοποιημένη, διπλά τυφλή ελεγχόμενη κλινική μελέτη που είχε ως δείγμα υπέρβαρες και παχύσαρκες γυναίκες στις οποίες χορηγήθηκαν 2 γραμμάρια ωμέγα λιπαρών (EPA και DHA) ή το αντίστοιχο εικονικό χάπι. Η στατιστική ανάλυση έδειξε ότι στην ομάδα παρέμβασης οι εθελόντριες είχαν ελαττωμένα επίπεδα CRP στο πλάσμα σε σύγκριση με την ομάδα ελέγχου, ενώ δε παρατηρήθηκε καμία άλλη διαφορά στους υπόλοιπους βιοχημικούς δείκτες που μετρήθηκαν. Αυτά τα ευρήματα δείχνουν ότι η χορήγηση ωμέγα 3 λιπαρών για >25 εβδομάδες συνδέεται με μείωση της φλεγμονής στο λιπώδη ιστό της μητέρας και στον πλακούντα, με τους TLR4 υποδοχείς να αποτελούν όπως φαίνεται τον κύριο στόχο δράσης των αντιφλεγμονωδών ωμέγα 3 λιπαρών. Συμπερασματικά, η χορήγηση ωμέγα 3 λιπαρών οξέων πιθανόν να αποτελεί σημαντική παρέμβαση στην εγκυμοσύνη για την υγεία της μητέρας και του εμβρύου, λόγω της προστατευτικής τους δράσης έναντι της φλεγμονής.

Λέξεις ευρετηρίου: ωμέγα 3 λιπαρά οξέα, φλεγμονή, παχυσαρκία, εγκυμοσύνη

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