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Omega-3 fatty acids during pregnancy and asthma prevention. Are we talking here about more than just a suspect involved?

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English key words: fatty acids, omega-3, pregnancy, asthma, child, preschool.

Spanish key words: ácidos grasos omega-3, embarazo, asma, preescolar.

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Omega-3 fatty acids during pregnancy and asthma prevention. Are we talking here about more than just a suspect involved?

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Original article: FBisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos AM, *et al.* Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. *N Engl J Med.* 2016;375:2530-9.

Abstract

Authors' conclusions: supplementation with n-3 long chain polyunsaturated fatty acids in the third trimester of pregnancy reduced the absolute risk of persistent wheeze or asthma and infections of the lower respiratory tract in offspring by approximately 7 percentage points, or one third.

Reviewers' commentary: although the results of this clinical trial indicate a preventive relationship between omega-3 fatty acid supplementation and asthma development, detected limitations (cointerventions and differences in other asthma-related risk factors) and discrepancies with other studies, do not support supplementation of pregnant women for this purpose.

Key words: fatty acids, omega-3, pregnancy, asthma, child, preschool.

Ácidos grasos omega-3 durante el embarazo y prevención del asma, ¿algo más que un presunto implicado?

Resumen

Conclusiones de los autores del estudio: la suplementación durante el tercer trimestre de embarazo con ácidos grasos poliinsaturados de cadena larga omega-3 redujo el riesgo de los hijos de presentar sibilancias persistentes o asma, e infecciones del tracto respiratorio inferior.

Comentario de los revisores: aunque los resultados de este ensayo clínico indican relación de prevención entre la suplementación con ácidos grasos omega-3 y un menor desarrollo de asma, las limitaciones detectadas (cointervenciones y diferencias en otros factores de riesgo relacionados con el asma) y las discrepancias con otros estudios, no apoyan suplementar a las gestantes con esta finalidad.

Palabras clave: ácidos grasos omega-3, embarazo, asma, preescolar.

STRUCTURED ABSTRACT

Objective: to assess whether supplementation with long-chain omega-3 long-chain polyunsaturated fatty acids (n-3 LCPUFAs) during the third trimester of gestation reduces the risk of persistent wheezing and asthma in the offspring.

Design: double-blind randomised controlled clinical trial.

Setting: Herlev and Gentofte Hospital, University of Copenhagen.

Study sample: 736 women were recruited at 22 to 26 weeks' gestation for the clinical trial. Their children form the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort (COPSAC2010). Participants completed a food frequency questionnaire, and their blood levels of eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) were measured before randomisation and one week after delivery. After delivery, the resulting cohort consisted of 695 children; 95.5% completed the initial three-year followup and 647 (93.1%) the full five years' followup.

Intervention: starting at 24 weeks' gestation, women in the treatment group received a daily supplement of 2.4 g of n-3 LCPUFAs (containing 55% EPA and 37% DHA). The control group received olive oil. A subgroup of 623 women also participated in a trial with a nested factorial design and took 2400 IU of vitamin D3 during the third trimester; a subgroup of 51 women participated in an influenza vaccine trial, and a subgroup of 72 children with persistent wheezing participated in a trial in which they took azithromycin or placebo during asthma episodes.

Outcome measurement: the primary endpoint was the diagnosis of persistent wheezing (before age 3 years) or asthma (starting at age 3 years). These diagnoses were made if the diary recordings included five episodes of lung symptoms within the preceding six months, each lasting at least three consecutive days; symptoms characteristic of asthma; the need for rescue therapy with β_2 -agonists; or response to a three-month course of inhaled glucocorticoids followed by relapse at the end of treatment. The secondary end points included lower respiratory tract infection (clinical diagnosis of bronchiolitis or pneumonia), asthma exacerbations, eczema and allergic sensitisation. Both investigators and participants were blind to group assignments in the first three years of followup, while between the third and fifth years only the researchers were unaware of group assignments.

Main results: the risk of persistent wheezing or asthma in the treatment group was lower compared to control group: 16.9% versus 23.7%, with a hazard ratio (HR) of 0.69; and a 95% confidence interval (95 CI) of 0.49 to 0.97. This effect was strongest in children of women with EPA and DHA levels in the lowest third at the time of randomisation: 17.5% versus 34.1% (HR, 0.46; 95 CI, 0.25 to 0.83). The risk of lower respiratory tract infection up to age 5 years was 38.8% in the treatment group compared to 45.5% in the control group (HR, 0.77; 95 CI, 0.61 to 0.99). The authors did not find an association with any of the remaining secondary end points.

Conclusion: supplementation with n-3 LCPUFAs in the third trimester of pregnancy reduced the risk of persistent wheezing, asthma and lower respiratory tract infection in the offspring.

Conflicts of interest: three of the authors disclosed activities in this section (Dr. Stark, Dr. Bisgaard and Dr. Bonnelykke).

Funding source: COPSAC is financed by a combination of public and private funds (www.copsac.com).

COMMENTARY

Justification: fish is the main source of n-3 LCPUFAs. Multiple clinical trials have been performed to assess the effect of supplementation with n-3 LCPUFAs in pregnant women on gestation and the offspring. When it comes to its association with asthma prevention, research has found variable results.^{1,2}

Validity or scientific rigour: when it came to internal validity, the clinical question was clearly defined. Random allocation was performed with a concealed sequence and a full followup was carried out. Participants and researchers were both blinded. There were some limitations, such as an adherence to treatment of less than 80% in 29% of participants, or the presence of various co-interventions, such as the administration of vitamin D. Although the results remained unchanged in the adjusted analysis, the stratified analysis showed that the effect of n-3 LCPUFAs was only observed when the control group did not receive vitamin D supplementation. Considering that vitamin D is used for asthma prevention and control,³ it cannot be ruled out that the protective effect of co-intervention (vitamin D) affected the results. The Bayesian model found factors with a stronger association with asthma development, such as maternal smoking and preterm birth, than supplementation with n-3 LCPUFAs.

The main limitation in its external validity is that the sample consisted of Caucasian women with a daily intake of fish that exceeded the consumption reported in other countries, with a high prevalence of self-reported asthma, eczema or allergic rhinitis (30%, 21% and 38%) and of high socioeconomic status.

Clinical relevance: this study supports the protective effect of n-3 LCPUFAs supplementation against the development of asthma in children, with a number needed to treat (NNT) of 14.6 and a larger effect size in pregnant women with lower baseline levels of EPA and DHA. In a randomised controlled trial (RCT) published by Olsen in 2008,¹ the HR of the group that received a fish oil supplement also suggested a protective effect against allergic asthma (HR, 0.13; 95 CI, 0.03 to 0.60). When it came to fish intake, there was a significant association between low intake and asthma and atopic dermatitis (HR, 0.10; 95 CI, 0.01 to 0.87). A 2015 Cochrane review² did not find differences in the development of asthma or wheezing in children aged more than 36 months based on supplementation with n-3 LCPUFAs or fish oil during pregnancy, breastfeeding or both (relative risk [RR], 1.10; 95 CI, 0.34 to 3.58). In terms of safety, there was no increase in maternal postpartum haemorrhage nor a higher incidence of fever or infection in children. Best *et al*⁴ reviewed observational and experimental studies with inconsistent results. In the former, low fish intake was associated with asthma development, while the rest did not find an association between low fish intake or supplementation with n-3 LCPUFAs and the development of asthma or wheezing. A RCT conducted by the same author⁵ that has been reviewed in this journal⁶ did not find differences in the risk of developing asthma or IgE-mediated wheezing in the six-year followup.

Applicability to clinical practice: the findings of this study do not suffice to recommend supplementation with n-3 LCPUFAs during pregnancy for the purpose of preventing asthma. To reach more conclusive findings, additional well-designed RCTs need to be conducted to confirm whether this protective effect does in fact exist, and assess potential differences between subgroups with a lower intake of fish.

Conflicts of interest: the authors of the commentary have no conflicts of interest to declare.

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