Original Article

Prenatal Intake of Vitamins and Allergic Outcomes in the Offspring: A Systematic Review and Meta-Analysis

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What is already known about this topic? Few observational studies suggest that vitamin deficiency is associated with developing higher prevalence of allergic diseases in children; however, we need robust evidence from randomized controlled trials to determine if this is the case.

What does this article add to our knowledge? This systematic review indicates that prenatal intake of vitamin D may protect against the development of recurrent childhood wheeze. Because early childhood wheeze is not necessarily the same as asthma, longer-term follow-ups of these trials are required to establish the efficacy of vitamin D in the prevention of actual asthma in later childhood.

How does this study impact current management guidelines? Consumption of higher doses of vitamin D during pregnancy needs to be considered in pregnancy management policies. However, the effective dose could vary depending on the baseline level of vitamin D in different regions.

BACKGROUND: Allergic diseases have seen a rise worldwide, with children suffering the highest burden. Thus, early prevention of allergic diseases is a public health priority.
OBJECTIVE: To synthesize the evidence from randomized controlled trials (RCTs) assessing the effect of vitamin interventions during pregnancy on developing allergic diseases in offspring.
METHODS: We searched CENTRAL, MEDLINE, SCOPUS, World Health Organization's International Clinical Trials Registration, E-theses, and Web of Science. Study quality was evaluated using Cochrane's risk of bias tool. Included RCTs had a minimum of 1-month follow-up postgestation.
RESULTS: A total of 5 RCTs met the inclusion criteria, including 2456 children who used vitamins C + E (1 study), vitamin C (1 study), and vitamin D (3 studies) compared with placebo/control. Two studies were judged to have a high risk of bias for performance bias or a high rate of loss to follow-up. All were rated as low risk of bias for blinding of outcome assessment. We did not perform meta-analysis with vitamin C or vitamin C + E studies due to high heterogeneity between the 2 included studies. However, we did conduct a meta-analysis with trials on vitamin D (including 1493 children) and the results showed an association between the prenatal intake of vitamin D and the risk of developing recurrent wheeze in offspring (relative risk (RR), 0.812; 95% CI, 0.67-0.98).
CONCLUSIONS: The current evidence suggests that prenatal supplementation of vitamin D might have a beneficial effect on recurrent wheezing in children. Longer-term follow-up of these studies is needed to ascertain whether this observed effect is sustained. There is lack of evidence on the effect of other vitamins for the prevention of respiratory and/or allergic outcomes. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Vitamins; Allergic outcomes; Asthma; Wheeze; Wheezing; Respiratory outcomes; Eczema; Offspring; Clinical trial; Intervention; Efficacy; Effectiveness; Systematic review; Meta-analysis*

In the last 2 decades, allergic diseases have seen a rise worldwide, with children suffering the highest burden of the condition.[1] Food allergies, eczema, and asthma are the most common allergic disorders in children.[1,2] Because of the increasing burden of allergic diseases, they are a key focus for public health.

The Developmental Origins of Health and Disease theory proposes that development is not dictated by a hard-wired genetic program; instead, the organism responds to the surrounding environment and the risk of many diseases is set during this time.[3] It has become increasingly evident that there is an important role for environmental factors in the onset of complex conditions such as allergic diseases and that the role of fixed

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Abbreviations used
HR- Hazard ratio
RCT- Randomized controlled trial
RR- Relative risk

genetic variation is far less than previously believed.[4] Therefore, new approaches toward disease prevention with an emphasis on early interventions, that is, prepregnancy and/or during pregnancy, need to be widely investigated. Current evidence suggests that the role of maternal diet during pregnancy in subsequent disease development is a priority area for future studies,[5] because many of the immune modulatory processes may start *in utero*.

The role of environmental and lifestyle factors in developing allergies has been examined in a number of epidemiological studies. A systematic review has investigated the association of nutrient deficiencies with the risk of development of asthma and allergic diseases in children.[6] This review included 62 observational studies and indicated that vitamins A, D, and E; zinc; fruits and vegetables; and a Mediterranean diet during pregnancy may prevent asthma and wheeze. However, this review was based on observational studies, which carry a high risk of bias, and there is a need for secondary research based on summary of more robust interventional studies.

The purpose of this systematic review was to summarize the existing evidence from randomized controlled trials (RCTs) for the association between intake of vitamin supplements during pregnancy and the risk of developing allergic disorders in the offspring.

METHODS

Criteria for considering studies for this review

Types of studies. Only RCTs (including cluster RCTs and quasi-RCTs) with a minimum follow-up of 1 month postnatally were included. The review considered studies that documented clinical outcome data and used any types of vitamins. No language restriction was applied.

Types of participants. Pregnant women and their offspring, regardless of their location, were considered as the target group for this systematic review. High-risk populations were not excluded.

Types of interventions. Studies that used any vitamin supplementation during pregnancy, irrespective of dose, formulation or mode of delivery, and composition, for example, oil and tablet, were included.

Trials were also included if the intervention(s) had been extended after pregnancy either during breast-feeding or with the infants or both.

Outcomes of interest. Trials were included if they had reported clinical outcomes of allergy in the offspring, either as a primary end point or as a secondary end point. Allergic outcomes were defined as asthma, wheeze, rhinitis, eczema, food allergy, and positive skin prick test result (to any allergen) and elevated specific IgE level. Outcomes included were those that had used a validated method as opposed to parental reports.

Search strategy for identification of studies. A comprehensive search strategy, including all the relevant synonyms for the main concepts, was developed covering the main bibliographic databases (see this article's Online Repository at www.jaci-inpractice.org). Trials were identified through systematic searches within 3 main electronic databases, as advised by the Cochrane collaboration[7]:

a. Cochrane Library (current issue) including the following:
   - Cochrane Database of Systematic Reviews (CDSR)
   - CENTRAL (trials)
   - Database of Reviews of Effectiveness
b. MEDLINE (EBSCOhost)
c. SCOPUS

When searching MEDLINE, the subject-specific terms were combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximising version.[7] We adapted the preliminary search strategy for MEDLINE (EBSCOhost) for use in the other databases when relevant. The last search for literature was conducted in January 2016.

The clinical trials registry and World Health Organization platform were searched for ongoing and recently completed trials. Conference proceedings were identified through the Institute for Scientific Information Web of Science, and the British Library E-Theses Online Service was searched for retrieving theses. No language or publication status restrictions were imposed. References of included studies were crosschecked for additional studies.

Data collection and analysis

Selection of studies. The main reviewer (M.V.) screened all the search results against the eligibility criteria and all those that were clearly irrelevant were excluded from further consideration. Thereafter, a tailored eligibility form was used by M.V. to appraise the retrieved studies, abstract, and full text for relevance against the full inclusion criteria. Where there was uncertainty about the inclusion of a particular study, other members of the review team (H.M. and T.D.) were consulted and a consensus was reached about the study eligibility. All the included studies were discussed and approved by the review team.

Data extraction. M.V. extracted the data using a tailored data extraction form (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Detailed information on study characteristics was recorded. Throughout the data extraction process, any disagreements about the interventions and outcomes were discussed and resolved within the review team. There was no blinding to the name of authors, institutions, journals, or the outcomes of the trials during the process. Ten percent of all the extracted data was randomly selected and double checked by a second reviewer (H.M.) for accuracy against the trial reports.

Assessment of risk of bias in included studies. The risk of bias tool described in the Cochrane Handbook for Systematic Reviews for Interventions was used to appraise the studies.[8] The tool includes 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other bias.

Measurement of treatment effect

Dichotomous data were analyzed as relative risk (RR) with 95% CI and continuous data as mean difference or standardized mean difference, with 95% CI.