Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases

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CRD summary
This review concluded that partially hydrolysed formula was effective, compared with standard formula, in preventing allergy in children at high risk, at most time points, but these findings should be interpreted with caution due to methodological concerns. There were some issues with the trials, but this was generally a well-conducted review and the authors' cautious conclusions appear to be appropriate.

Authors' objectives
To assess the safety and efficacy of a partially hydrolysed 100% whey formula, in reducing the risk of allergy, in healthy infants who were at a high risk of allergy.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and CINAHL were searched for articles from inception to September 2009, without language restrictions. The search terms were reported. Reference lists from retrieved articles and key review articles were manually searched. The manufacturer of partially hydrolysed formula was contacted for unpublished data. Published letters to the editor, abstracts, and proceedings from scientific meetings were only included if a full set of data could be obtained from their authors.

Study selection
Randomised controlled trials (RCTs) and quasi-RCTs were eligible for inclusion if they compared partially hydrolysed formula (manufactured by Nestle) with a standard infant formula or an extensively hydrolysed formula, containing hydrolysed bovine proteins (whey or casein), for prevention of allergies in healthy full-term infants who were at a high risk of developing an allergy. The risk of developing an allergy was assessed by the family history and other markers, which were described. The primary outcomes were all allergic diseases, and atopic eczema or atopic dermatitis. Secondary outcomes were respiratory symptoms, allergic rhinitis, food allergy or hypersensitivity, urticaria, and anaphylaxis.

Included trials were conducted in industrialised countries and, where reported, interventions lasted from three to 12 months. Definitions of atopic eczema or atopic dermatitis varied between trials. Some trials assessed formula in addition to breast feeding, and one assessed formula in addition to weaning food after a certain time period. Some trials included co-interventions, such as dietary restrictions, or the avoidance of tobacco smoke, pets, and damp housing conditions.

Two reviewers independently screened articles for inclusion and discrepancies were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed the quality of the included trials, using the Cochrane Collaboration's tool for assessing risk of bias, which includes criteria for the adequacy of sequence generation, allocation concealment, blinding, completeness of follow-up data, and bias from selective outcome reporting and other sources. Each criterion required a yes (indicating a low risk of bias) or no (indicating a high risk of bias) response.

Data extraction
The number of participants who experienced each outcome was extracted to calculate risk ratios and their 95% confidence intervals. Trial authors were contacted for further data, where necessary. The data were extracted by one reviewer and checked by a second, with discrepancies resolved through consensus.

Methods of synthesis
Fixed-effect and random-effects models were used to pool the risk ratios and their 95% confidence intervals. The
numbers needed to treat were also calculated. Heterogeneity was assessed using the X$^2$ and I$^2$ statistics. The authors intended to assess publication bias, using a funnel plot.

Subgroup analyses were undertaken on the incidence and cumulative incidence of allergic diseases and eczema, in several age groups and by per protocol or intention-to-treat analysis. Sensitivity analyses were conducted to remove trials with low methodological quality, which were those with unclear or inadequate methods of randomisation or allocation concealment.

**Results of the review**

Twelve RCTs, in 15 publications and with 3,284 patients, were included. Sample sizes ranged from 30 to 2,252 patients. Follow-up ranged from six months up to six years. One trial was assigned yes to four criteria on the validity scale (adequate sequence generation, allocation concealment, blinding, and incompleteness of outcome data addressed) and one trial was assigned yes to three criteria. The remaining trials were assigned unclear or no, for most of the criteria, which indicated a high risk of bias.

**Allergic diseases** (seven RCTs): Using a random-effects model, partially hydrolysed formula was statistically significantly more effective in reducing the risk of all allergic diseases (incidence) compared with standard formula at three to six months (RR 0.48, 95% CI 0.23 to 1.00; five RCTs); at one year (RR 0.62, 95% CI 0.45 to 0.85; NNT=12; four RCTs); and at 30 to 36 months (RR 0.42, 95% CI 0.19 to 0.90; one RCT); but not at two years (two RCTs). There was evidence of statistical heterogeneity at three to six months (I$^2$=58%).

**Atopic dermatitis or atopic eczema** (eight RCTs): Using a random-effects model, partially hydrolysed formula statistically significantly reduced the incidence of eczema compared with standard formula at one year (RR 0.68, 95% CI 0.48 to 0.98; I$^2$=0%; four RCTs); but not at four to six months (five RCTs), two years (three RCTs), nor 30 to 36 months (two RCTs).

There were no statistically significant differences between partially hydrolysed formula and extensively hydrolysed whey formula nor extensively hydrolysed casein formula in the risk reduction for all allergic diseases nor for atopic dermatitis or atopic eczema (these data were available from the authors upon request). The cumulative incidence of all allergic diseases and eczema were reported, along with the secondary outcomes.

Sensitivity analyses did not significantly alter these results (these data were also available on request).

**Authors’ conclusions**

Partially hydrolysed formula was effective, compared with standard formula, in preventing allergy, particularly atopic dermatitis or atopic eczema, in children at a high risk of allergy, at most time points, but these findings should be interpreted with caution due to methodological concerns.

**CRD commentary**

The review question and inclusion criteria were clearly defined. A comprehensive literature search was undertaken, without language restrictions, and included attempts to locate unpublished data, reducing the potential for language and publication bias. Validity was assessed using appropriate methods, but the quality of the included trials was generally low. The authors pointed out that their findings should be interpreted with caution as many of the trials had poor methods. Each stage of the review process was carried out in duplicate, which minimised the potential for reviewer error and bias. Appropriate methods appear to have been used to combine the data and to test for statistical heterogeneity, but there was evidence of statistical heterogeneity for some comparisons. The authors acknowledged that there was some variation in the definitions of conditions, which made it difficult to directly compare the trials, and that some trials had small samples. Some of the comparisons also included only a small number of trials and some trials included co-interventions and it was unclear how these might have affected the findings. These findings related only to the partially hydrolysed formula that was manufactured by Nestle, and Nestle funded this review.

This was a generally well-conducted review and the authors’ cautious conclusions appear to be appropriate.
Implications of the review for practice and research

Practice: The authors stated that their findings were generalisable, because the included trials were conducted in a variety of settings, but only to infants and children at a high risk of developing allergic disease.

Research: The authors stated that further research was required to assess the cost-effectiveness, the most effective duration, and the long-term effects of partially hydrolysed formula, and to determine who would gain the most clinical benefit; infants at high risk of allergy or all infants.

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