

Systematic review with meta analysis

Study finds little impact of hydrolysed formula on risk of allergic disease, but study methods may limit conclusions and generalisability

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Commentary on: Boyle RJ, Ierodiakonou D, Khan T, *et al*. Hydrolysed formula and risk of allergic or autoimmune disease: systematic review and meta-analysis. *BMJ* 2016;352:i974.

Context

Several meta-analyses, including a Cochrane analysis, performed previously on the same topic, came to the conclusion that 'hydrolyzed formula is recommended in the first 4–6 months of life for the primary prevention of allergic diseases'.^{1–3} In 2012, the Food and Drug Administration (FDA) concluded that a particular partial whey hydrolysate could reduce the risk of eczema in high-risk infants. Boyle and colleagues, however, come to a different conclusion, and state that the current guidelines recommending hydrolysates to prevent allergic disease in high-risk infants are not supported.

Methods

This meta-analysis included data from 37 intervention trials including over 19 000 participants. The review was performed in accordance with PRISMA guidance. Heterogeneity and publication bias were assessed.

Findings

According to the authors, there was evidence of conflict of interest and risk of publication bias in most studies of allergic outcomes, eczema and wheeze. Overall, there was no consistent evidence that partially or extensively hydrolysed formulas (eHFs) reduce risk of allergic or autoimmune outcomes in infants at high pre-existing risk of these outcomes. ORs for eczema at age 0–4 months, compared with standard cows' milk formula, were 0.84 (95% CI 0.67 to 1.07; $I^2=30\%$) for partially hydrolysed formula (pHF); 0.55 (0.28 to 1.09; $I^2=74\%$) for extensively hydrolysed casein based formula; and 1.12 (0.88 to 1.42; $I^2=0\%$) for extensively hydrolysed whey-based formula.

Commentary

Several methodological factors explain why this meta-analysis draws different conclusions than previous ones. The authors used broad selection criteria, including studies of any type of hydrolysed formula, compared to any other type of infant feeding. All pHF and eHF trials,

independent of the methodological quality, were included. pHFs and eHFs differ significantly in composition, methods and degree of hydrolysis. Some of the hydrolysates studied were never commercialised. The meta-analysis includes two trials that had not been included in previous reviews: an Australian trial published in 2011 and the trial that was recently published by the same authors. The Australian trial found no effect of pHFs, but only 50% of infants received some of the allocated formula by 4 months of age, while 16.5% never received their allocated formula. The prebiotic enriched pHF was said to not reduce atopic dermatitis, but data in the control breastfed group were not shown. The intervention stopped at the age of 6 months but outcome was reported at 12 months. In addition, the authors cluster atopic outcomes by specific age groups: 0–4, 5–14, 15–24 months, for example, without providing a clinical rationale. For some conditions such as atopic dermatitis, a smaller age range is likely needed to show clinically relevant effects. Differences in genetic background may also contribute to the differences observed. Findings of meta-analyses differ based on the predefined inclusion parameters, statistical methods used and set outcomes.

Implications for practice

Exclusive breast feeding is the gold standard to feed infants. Formula feeding is the second choice for infant feeding. Cow's milk protein sources have historically been chosen simply because there are many cows and cows provide substantial milk, not because the composition of cow's milk is close to that of mother's milk. While there is some evidence that specific hydrolysates can reduce the risk of atopic dermatitis, particularly in infants with familial atopic history, this evidence disappears if all hydrolysates and all clinical trials are analysed together. Hydrolysates are a safe option to feed infants. pHFs have been approved by the FDA, European Food Safety Administration and the European Commission for use as routine infant formula protein options for any healthy infant.⁴ There is not a single study suggesting that a hydrolysate may cause more allergy than infant formula with intact protein. Thus, finally, whether to use a hydrolysate is a cost-benefit discussion that depends on individual factors. Overall, given the variable findings of this and previous meta-analyses of hydrolysates in infant feeding, there is still a need for future high quality, prospective, independently funded trials of the impact on allergic disease.

Competing interests YV has participated as a clinical investigator and/or advisory board member and/or consultant and/or speaker for Abbott Nutrition, Aspen, Biogaia, Biocodex, Danone, Hero, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Merck, Orafit, Phacobel, Rontis, Sari Husada, United Pharmaceuticals, Wyeth and Yakult.

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