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EDITORIALS

Do hydrolysed infant formulas reduce the risk of allergic disease?

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With no supporting evidence, guidelines should stop recommending these products

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Breast feeding is the first and most important feeding exposure, and it facilitates the establishment of the microbiome of the infant gut by providing breast milk microbiota, immunomodulatory factors, and oligosaccharides.¹ While there is insufficient evidence to state that breast feeding prevents allergies,² it seems to prevent a range of other diseases and is universally encouraged.³ Guidelines advocate exclusive breast feeding for four to six months (with WHO recommending six months) and complementary feeding for at least one to two years. Breast milk substitutes are used on cessation of established breast feeding or earlier if mothers cannot breast feed. The quality of these substitutes, and their ability to play a role in optimal health and disease prevention, are of intense interest, both to the public and also to commercial entities keen to produce an acceptable and safe alternative to breast milk.

A linked systematic review by Boyle and colleagues (doi:10.1136/bmj.i974) investigates whether hydrolysed cows' milk formulas can prevent allergic or autoimmune disease.⁴ The term "hydrolysed" is used to describe proteins that have been broken down by enzymes into smaller, less allergenic, peptide fragments. Infant feeding guidelines in Europe, America, and Australasia⁵⁻⁷ support the use of hydrolysed formulas in place of standard cows' milk formula if the infant is not breast fed for the prevention of allergic disease in children at increased risk, despite ongoing debate as to whether there is sufficient evidence to support this recommendation.

Boyle and colleagues conducted a comprehensive review using rigorous methods. It supersedes the previous and now outdated Cochrane review by Osborn and Sinn on this topic.⁸ Osborn and Sinn found "limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant CMA [cows' milk allergy]." In contrast, by including the most recent evidence and through a critical appraisal of the literature, Boyle and colleagues found "no consistent evidence that partially or extensively hydrolysed formulas reduce risk of allergic or

autoimmune outcomes" and highlighted the low quality of evidence. On the basis of these findings, they ask for changes to current infant feeding guidelines that recommend the use of these formulas.

A major strength of the current review is its assessment of all included studies for quality, along with an overall assessment of the quality of evidence from each meta-analysis by using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria.⁹ The GRADE criteria provide a framework for a systematic approach to both rating the quality and strength of the evidence derived from systematic reviews and developing recommendations from this evidence. Boyle and colleagues emphasise that many of the trials investigating the effect of hydrolysed formulas on risk of allergic disease have a high or unclear risk of bias because of conflicts of interest related to sponsorship from industry. Given the commercially sensitive nature of this topic, it is reassuring that, when it was possible to investigate, they did not find evidence that these conflicts of interest influenced the reported associations for individual outcomes. With increasing and necessary involvement of industry in medical science it is imperative that we take steps to ensure transparency and prevent commercial priorities from influencing published results.

While experts might recognise the lack of evidence for the effectiveness of hydrolysed formulas in prevention of allergies, it seems that these formulas are currently recommended in the hope that they might prevent allergic disease and on the basis that they are unlikely to do any harm. The most undesirable consequence of this approach is that it can unwittingly undermine efforts to promote breast feeding. We know that formula feeding, whether the formula is hydrolysed or not, cannot replicate the complex and adaptive constituents of breast milk and the benefits of breast feeding for mothers or babies.³ Advice from medical personnel and mothers' perceptions of breast feeding can be altered by advocacy for particular types of formula within infant feeding guidelines. Secondly, endorsing

hydrolysed formulas as an effective means to prevent allergies undermines attempts to conduct further more robust and definitive research on this issue. Finally, accepting that a particular formula prevents allergy based on poor quality evidence hinders further efforts by formula producers to improve their products.

It is now time for this evidence to be used for updating and clarifying current recommendations and guidelines. Furthermore, we encourage industry to pursue development of effective allergy reducing infant formulas and call for further transparent and well conducted studies in this area.

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