

EDITORIAL

Clinical & Experimental Allergy

Primary prevention with hydrolysed formula: does it change natural onset of allergic disease?

This editorial discusses the findings of the paper by Berg et al. [10] pp. 627–636.

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There is some evidence to support the use of infant dietary interventions for prevention of allergy, particularly eczema in infants. Several Cochrane Systematic Reviews [1–4] have examined evidence for use of various interventions and reported that use of a partially hydrolysed or extensively hydrolysed infant formula may prevent allergy in infancy. There is no evidence of benefit from use of a soy formula [1] and inadequate evidence to date to determine the allergy preventing effects of probiotics and prebiotics [3, 4] added to infant feeds. Evidence of benefit from use of a hydrolysed formula is largely restricted to infants at high risk based on family history [2]. Several meta-analyses of observational studies [5, 6] and a cluster randomized trial of breastfeeding support measures [7] provide some evidence that exclusive breastfeeding may be effective in preventing infant eczema as well as gastrointestinal infections. Based on current evidence, several societies [8, 9] have recommended allergy prevention policies that include use of a partially hydrolysed formula if there is inadequate breast milk for infants with a positive family history of allergy.

In this issue, the GINIplus study is reported with outcomes up to 6 years of age [10]. In the original GINI study [11], 2252 infants at high risk of allergy based on a first-degree family history of allergy were randomized to one of the four study formulas – a cow's milk formula, a partially hydrolysed whey formula, an extensively hydrolysed whey and an extensively hydrolysed casein formula. In intention-to-treat analyses, several publications of the GINI study [11–13] with follow-up to 6 years have reported a significant reduction in infant eczema in

infants fed an extensively hydrolysed casein but not the other types of hydrolysed formula compared with use of a cow's milk formula. However, these results should be viewed in the context of all the evidence. The Cochrane review [2] reported methodological concerns with almost all studies, with the GINI study reporting between 10% and 20% losses to follow-up at various time-points. The overall meta-analyses found a significant reduction in infant allergy from use of a hydrolysed formula, with some evidence of benefit from both an extensively hydrolysed for prevention of eczema and a partially hydrolysed formula for prevention of all allergy although there is some heterogeneity in meta-analysis findings.

The report in this issue is rather complex [10], reporting a modified intention to treat analysis of the GINIplus study. It includes infants at high risk of allergy randomized to different formulas, but also those infants not randomized. The non-randomized infants include groups that were low risk, therefore not eligible for randomization, as well as non-randomized high-risk infants. To complicate the report further, randomized high-risk infants who were non-compliant with treatment are reported separately. There is an attempt to adjust for non-comparable groups by using regression techniques. Dropout rates averaged 23%. Given the modified intention-to-treat analysis, for which there is empirical evidence for bias from this practice [14], it is difficult to determine if much can be concluded from the results of this complicated analysis. However, in brief, the authors report that the findings largely confirm the findings of their other reports. High-risk infants are more likely to develop allergy than low-risk infants, and only the intervention group fed an extensively hydrolysed casein formula were not at significantly increased risk of allergy diagnosis or symptoms compared with the low-risk non-intervention group. High-risk infants fed partially or extensively hydrolysed whey based formulas or a cow's milk formulas were still at significantly increased risk of

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allergy. Of interest is that the non-compliant group were also at significantly increased risk. We will never know whether this is due to their lack of compliance or whether non-compliance was related to allergy symptoms. However, excluding this group from an intention to treat analysis has created the potential for bias [14].

The GINIplus study provides intriguing evidence that should guide the choice of hydrolysed formula type for future studies. The Cochrane review [2] reinforces this and concludes that in view of methodological concerns and inconsistency of findings, further large, well-designed trials comparing formulas containing partially hydrolysed whey, or extensively hydrolysed casein to cow's milk formulas are needed in high-risk infants unable to be exclusively breastfed.

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