

CORRESPONDENCE

Clinical and Experimental Allergy

Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization

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With great interest, we have read the article by Huurre et al. [1] reporting on the impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization. We would like to comment on some of the results of this trial.

First, the authors found an increased risk of sensitization in infants with allergic mothers breastfeeding over 6 months or exclusively breastfeeding over 2.5 months. Therefore, they conclude that breastfeeding in atopic mothers is a risk factor for sensitization in infants. However, these results may be biased, because of reversed causation [2]. The authors give no information regarding the prevalence of allergic disease, specifically atopic dermatitis, in the participating infants. It seems likely that the presence of allergic symptoms caused mothers to continue breastfeeding for a longer period of time, which could explain the observed relation between breastfeeding and increased sensitization.

Second, considerable attention is given to the observation that TGF- β 2 was higher in the probiotic than in the placebo group. However, this difference did not reach significance (CI, 0.96–2.34; $P=0.073$). Moreover, this moderate effect was seen only in the colostrum sample and had totally disappeared after 1 month, despite that the probiotic supplementation was still continued at that time. Therefore, it is questionable if probiotic supplementation actually changed the breast milk cytokine pattern.

Finally, we regret that no faecal samples of the mothers were analysed to confirm actual colonization with the given probiotic strains. This would have given important information on compliance.

References

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Response by Anu Huurre, on behalf of the NAMI (Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota) research group

We thank van der Aa et al. for their interest in our study, *Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: A double-blind placebo-controlled study*, evaluating possible factors explaining the protective effect of probiotics.

The questions van der Aa et al. have brought up concerns the secondary outcomes, not the main outcome of the study, i.e. that the protective potential of the combination of *Lactobacillus rhamnosus* strain GG and *Bifidobacterium lactis* Bb12 was best seen in high risk group of infants.

We agree with van der Aa et al. that the secondary outcomes may have received disproportionate attention in the final version; in the version originally submitted they were not equally emphasized. The reason why the reviewers wanted to stress these findings may be the fact that the results on breastfeeding are indeed in accordance with previous epidemiological data [1, 2]. Such epidemiological studies, however, clearly only document an association, not causality or reverse causality. This notwithstanding, we have previously studied the question in clinical studies [3, 4], revealing firstly that it can be

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problematic to breastfeed an infant manifesting atopic eczema already during exclusive breastfeeding, but despite the challenges, the recommended duration of 4–6 months can be achieved, but less frequently pro-longed breastfeeding [3]. Secondly, no uniform statement of breastfeeding *per se* can be given since the composition of breast milk is individual, reflecting the diet and the immunological balance of the mother. Allergic mothers seem, due to altered consumption of foods, to have higher amount of total fat and saturated fat in their diet as compared with healthy mothers and this seems to increase the risk of infant sensitization [4]. Finally, the risk of allergic diseases appears to be related to low concentrations of anti-inflammatory cytokines such as TGF- β 2 in breast milk [5] and this concentration can be increased by *L. rhamnosus* GG [6]. In the present study, the secondary result tended to support this original observation.

Concerning the detection of probiotic bacteria in faecal samples, although an attractive idea theoretically, we need to acknowledge that the current methods cannot reliably be applied for compliance testing. First, faecal samples fail to reflect the intestinal microbiota at the mucosal level; bacteria adhering to the mucosa are present in different compositions and concentrations when compared with faecal samples [7, 8]. Second, specific probiotic strains such as *L. rhamnosus* GG have been demonstrated to be present in mucosal biopsies much longer than in faeces [7, 10]. Thus, the testing of faecal samples alone is not sufficient in evaluating colonization by a probiotic strain.

Moreover, many probiotic effects are unlikely to be related to intestinal microbiota changes only and, additionally, we are not able to identify all changes in microbiota composition, especially the non-culturable microbiota. Indeed, an important part of the beneficial effects of probiotics is related to their immunomodulatory effects, immune-enhancing as well as anti-inflammatory activity. These topics are discussed in detail in recent reviews and reports of Isolauri et al. [11] as well as Cummings et al. [12].

In the present study, we discovered that the infants of allergic mothers, specifically those with the skin prick test reactivity, had a higher risk of sensitization at the age of 12 months. However, this risk could be reduced by means of probiotic supplementation during pregnancy and lactation. Thus, the critical period of pregnancy and

breastfeeding may be the window of opportunity in allergy prevention.

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