Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis

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CRD summary
This review concluded that there was a moderate benefit from probiotics in pregnancy and infancy in reducing the incidence of atopic and immunoglobulin E-associated atopic dermatitis. This was based on a substantial number of small-to-medium size double-blind randomised placebo-controlled trials. The conclusion appears reliable for atopic dermatitis but the evidence for immunoglobulin E-associated atopic dermatitis is less robust.

Authors' objectives
To assess whether probiotic use during pregnancy and early life decreased the incidence of atopic dermatitis and immunoglobulin E-associated atopic dermatitis in infants and young children.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched up to October 2011. The search strategy was reported. References of identified studies were also checked. Only published studies reported in English were eligible for inclusion.

Study selection
Randomised placebo-controlled trials that assessed one or more probiotics during pregnancy or infancy were eligible for inclusion. Trials had to assess the incidence of atopic dermatitis or immunoglobulin E-associated dermatitis measured before the age of 12 years, and to provide enough information to calculate relative risks with 95% confidence intervals. Trials that focused on the treatment rather than the prevention of dermatitis were excluded.

Most of the included trials were conducted in Europe; the rest were conducted in Australia, New Zealand and Asia. The most commonly used probiotic agent used was *Lactobacillus rhamnosus* GG, but a range of other probiotic types were given, either singly or in combination. Most trials used supplementation for the mother in the final weeks of pregnancy combined with supplementation for the child in the first few months of life. However, a range of approaches were adopted (including maternal only and infant only supplementation).

Two reviewers independently assessed the studies for inclusion; discrepancies were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed the trials for risk of bias using criteria including blinding, losses to follow-up and method of outcome assessment. Disagreements were resolved through discussion.

Data extraction
Data were extracted to calculate relative risks with 95% confidence intervals for atopic dermatitis and immunoglobulin E-associated atopic dermatitis in treatment compared with placebo groups. Severity of dermatitis was also assessed. Where multiple treatment arms were reported within a trial, they were combined into a single probiotic group. Early follow-up data was extracted based on the assumption that data were available for more patients.

Two reviewers extracted the data, with disagreements resolved through discussion.

Methods of synthesis
Pooled relative risks (with 95% confidence intervals) were calculated using both fixed-effect and random-effects analyses for atopic dermatitis and immunoglobulin E-associated atopic dermatitis. Heterogeneity was assessed using the $X^2$ test and inconsistency using the $I^2$.

Stratified analyses were conducted based on multiple factors including study location, intervention characteristics, family history and diagnostic criteria. Meta-regression was used to assess differences between subgroups where
Publication bias was assessed using visual examination of funnel plots and the tests of Begg and Egger.

Results of the review
Fourteen randomised controlled trials (RCTs) were included in the review. Thirteen RCTs (3,092 infants) assessed atopic dermatitis. Ten RCTs (2,711 infants) assessed immunoglobulin E-associated atopic dermatitis. There were insufficiently detailed data (11 trials) to assess severity of dermatitis. All trials were double-blinded and none showed differences in drop-outs between treatment and placebo groups. However, drop-out rates were over 20% in half the trials. Assessment was at between one and seven years of age; most used a follow-up period of one or two years. All except two trials reported outcome assessment by clinicians or trial personnel.

Children in the probiotic treatment groups had lower rates of atopic dermatitis than those in the placebo groups (RR 0.79, 95% CI 0.71 to 0.88; I²=24%; 13 RCTs; fixed-effect model). This was statistically significant with low levels of inconsistency between trials. A random-effects analysis did not materially alter the result; sensitivity analyses excluding trials with looser diagnostic criteria also did not change the estimate.

The evidence for a reduction in immunoglobulin E-associated atopic dermatitis was less clear. A fixed-effect analysis showed a statistically significant benefit with low levels of inconsistency (RR 0.80, 95% CI 0.66 to 0.96; I²=32%; 10 RCTs). However, the effect did not remain statistically significant in a random-effects analysis (RR 0.83, 95% CI 0.65 to 1.06).

Stratified analyses did not detect meaningful differences between subgroups. A larger estimate of effect in children with no family history of allergic diseases was based on only two trials.

There was no evidence of publication bias.

Authors’ conclusions
The meta-analysis provided evidence in support of a moderate role of probiotics in the prevention of atopic dermatitis and immunoglobulin E-associated atopic dermatitis in infants. The beneficial effect was similar regardless of the timing of probiotic treatment (during pregnancy or after delivery in early life) or who was treated (the breastfeeding mother, the infant or both).

CRD commentary
The review question was clear and supported by explicit inclusion criteria. The search was reasonable although the limitation to published studies in English had the potential for omitting relevant studies. There was no evidence that small trials with negative results had been missed, although the number of trials was relatively low for this analysis to be useful. The methods used were designed to reduce reviewer bias and error at every stage of the review process.

Some key criteria for trial reliability (risk of bias) were assessed, although other important aspects were not reported. The synthesis was appropriate and differences between trials were assessed. The authors’ conclusions reflected a relatively consistent benefit of probiotics on atopic dermatitis based on a substantial number of trials which were mostly small to medium in size. However, the evidence for an effect on immunoglobulin E-associated atopic dermatitis was less robust; the lack of a significant finding of benefit in the random-effects analysis should be taken into account.

The authors' conclusions appear reliable for atopic dermatitis but less so for immunoglobulin E-associated atopic dermatitis.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further studies should explore whether different probiotics have different effects on atopic dermatitis incidence, whether there was a moderation of effect by breastfeeding, and the mechanisms of effect.

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