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Five Probiotic Drops a Day to Keep Infantile Colic Away?

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Infantile colic is a common functional gastrointestinal disorder of early infancy characterized by long bouts of crying and hard-to-soothe behavior.¹ On average, the crying peaks at 6 weeks of age and then diminishes by 12 weeks of age.² Despite this self-resolving pattern, infantile colic has a substantial deleterious impact on society by negatively affecting parental health,³ resulting in decreased family functioning years later,⁴ with consultation for these issues leading to substantial health care expenditures.⁵ The immediate impact on the infant is unknown; they certainly do not seem happy. Ten years later, these infants with colic become children who have an 11-fold increased risk for developing recurrent abdominal pain, as well as an increased risk for allergic diseases and psychological disorders.⁶

The etiology of colic is unknown, although there is increasing interest in the potential relationship between the gut microbiome and this disorder. Differences in gut microbiome composition have been identified in colicky infants compared with healthy controls.⁷ However, as in disorders such as inflammatory bowel disease, it is less certain whether the altered gut microbiome is a cause or a consequence of the underlying condition. Among a number of factors, the gut microbiome can be influenced by diet and motility (transit time).⁸ Even the brain may influence the gut microbiome via the hypothalamic-pituitary axis and the autonomic nervous system, for example, by influencing factors such as motility and epithelial permeability.⁹ Alternatively, the gut microbiota can influence digestion of dietary nutrients and motility, as well as central nervous system functions.¹⁰ This forms the basis of the so-called brain-gut-microbiome axis.¹¹

Probiotics, as defined by the Food and Agricultural Organization of the United Nations and the World Health Organization in a joint consensus document, are live microorganisms that confer a health benefit on the host when administered in adequate amounts.¹² Various mechanisms of action have been proposed for probiotics, including enhancing epithelial barrier function, increasing IgA production, modulating cytokine profiles, influencing T lymphocytes, influencing other gut microbes, and affecting the enteric nervous system, that may result in changes in motility, pain perception, and brain activity.^{13,14} The ability of the microbiome (in part via diet) and probiotics to influence emotional functioning in humans may be one mechanism whereby probiotics may help alleviate the symptoms of colic.¹⁴

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A systematic review and meta-analysis published in this journal found that although probiotics show promise in the treatment and prevention of infantile colic, “there is still insufficient evidence to support the general use of probiotics in all infants with colic or to recommend its use in preventing colic.”^{15(p1156)} Within this meta-analysis are 3 small studies¹⁶⁻¹⁸ (with a total of 209 infants) that evaluated the use of *Lactobacillus reuteri* for colic treatment. Although all 3 trials showed a benefit in reducing crying time, there was significant heterogeneity among the studies.¹⁵ This might be expected, in part, because the same strain of *L reuteri* was not used in all studies and because different strains of the same bacteria may have different effects.¹⁹

In this issue of *JAMA Pediatrics*, Indrio et al²⁰ add a fourth double-masked, placebo-controlled randomized clinical trial of *L reuteri* to the literature using the same dose and strain (DSM 17938) as the studies by Savino et al¹⁶ and Szajewska et al.¹⁸ Unlike the previous studies, which treated infants with identified colic, Indrio et al²⁰ took a preventative approach and sought to determine if daily oral supplementation with *L reuteri* during the first 3 months of life (1×10^8 colony-forming units per day provided in 5 drops) could reduce crying time. In addition, the effect of the probiotic on regurgitation and constipation was also evaluated. In comparison with the other studies,^{16,18} both breastfed and formula-fed infants were enrolled. Infants received the therapy for 90 days, although it is not stated if the outcome at 28 or 90 days was the primary end point.

Indrio et al²⁰ are to be commended for carrying out a large, multicenter trial that included more infants than the previous 3 studies combined.¹⁶⁻¹⁸ The results of their study are encouraging. Indrio et al²⁰ found that crying time was significantly decreased and that bowel movements were more frequent at 28 and 90 days for those taking the probiotic vs controls. Regurgitation was found to be less frequent at 90 days only in those given probiotics. Even taking into account the cost of the probiotic, the probiotic group incurred fewer overall costs.

Although there are still many questions to be answered with respect to the use of *L reuteri* DSM 17938 (and other probiotics) for infantile colic, as well as with respect to their effect on gastrointestinal function (eg, gastroesophageal reflux), 2 critical areas are in need of investigation: the mechanisms of action and the effect on long-term health. There have been some attempts made at understanding the mechanisms of action of probiotics in infant colic. In an analysis of stool samples obtained from infants with colic, Roos et al²¹ found no changes in global microbiome composition in those infants taking *L reuteri* DSM 17938 vs those taking placebo, but the infants who were deemed to be responders (>50% decrease in crying time) had increases in *Bacteroides* at the end of the intervention period compared with those who were deemed nonresponders. Continued attempts at elucidation of the mechanisms of action may allow us to focus on particular probiotics that are likely to be effective and may potentially help us to identify those infants most likely to benefit from treatment.

Although studies on the use of probiotics for infantile colic have not identified adverse events to date,¹⁵ it is unclear how probiotic exposure in infancy may influence long-term health. Given the potential role of the gut microbiome in a number of disorders (eg, obesity)

and its ability to influence brain function as already outlined, their clinical use should be guided by well-done clinical studies. Ideally, participants should be reexamined several years after treatment to assess for potential long-term health consequences.

Nonetheless, despite their lack of information about the mechanisms of action and some study limitations, Indrio et al²⁰ lend additional support to the potential use of *L reuteri* DSM 17938 for infantile colic. Perhaps there will come a time when medical providers will recommend 5 probiotic drops a day to keep infantile colic away.

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