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REVIEW ARTICLE

Effect of lactase supplementation on infant colic: Systematic review of randomized controlled trials

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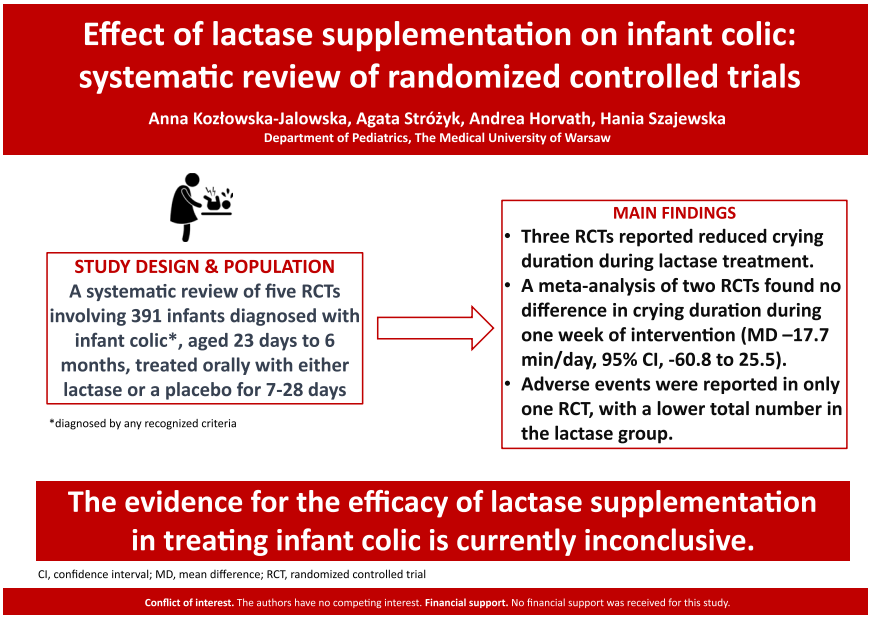
Abstract

To systematically review evidence on the efficacy and safety of using a lactase supplementation for managing infant colic. The MEDLINE, EMBASE, and Cochrane Library databases were searched (up to September 2023) for randomized controlled trials (RCTs) comparing oral lactase supplementation with placebo or no intervention in infants younger than 6 months old with infant colic. The risk of bias was assessed using the revised version of the Cochrane risk-of-bias tool. Outcomes measured were selected according to a standardized core outcome set. Five RCTs involving a total of 391 infants were identified. Three RCTs reported reduced crying duration, but one showed effect only in a compliant group (40.4%, $p = 0.0052$). A meta-analysis of two RCTs found no difference in crying duration and fussing time during 1 week of lactase treatment compared with placebo (mean difference [MD] −17.66 min/day, 95% confidence interval [CI], −60.8 to 25.5; $I^2 = 68\%$ and MD 2.75, 95% CI, −58.2 to 57.2; $I^2 = 80\%$, respectively). Other outcomes were assessed only in individual studies or not reported. The risk of bias was low in only one RCT, high in three, and raised some concerns in one. While individual trials have shown some promise, the overall evidence for the efficacy of lactase supplementation in treating infant colic remain inconclusive. Further well-designed RCTs are necessary to determine the effects of lactase on managing infant colic.

Abbreviations: 95% CI, 95% confidence interval; ITT, intention-to-treat; MD, mean difference; NNH, number needed to harm; NNT, number needed to treat; RCT, randomized controlled trial; RevMan, the Review Manager computer program (Version 5.4. The Cochrane Collaboration, 2020); RoB 2, the Cochrane Collaboration's risk-of-bias tool for randomized trials; RR, risk ratio.



KEYWORDS
children, excessive crying, lactose intolerance

1 | INTRODUCTION

Infant colic is a common gastrointestinal disorder affecting both breast-fed and formula-fed otherwise healthy children during the first months of life.[1] A 2017 systematic review summarized a frequency of infant colic that varied from 0.6% in infants aged 10-12 weeks to 25.1% in those aged 5–6 weeks.[2] The diagnostic criteria of infant colic have changed over the years.[3] Since 2016, the Rome IV Criteria have been recommended.[4] Previously, the Wessel criteria, also known as "the rule of three," were commonly used.[3] Although infant colic is not considered a serious clinical condition, some studies suggest it may be associated with parental distress, child abuse, and early breastfeeding cessation.[5] Recent studies also suggest that infant colic may lead to long-term issues including functional gastrointestinal disorders, migraine-type headaches, and behavioral problems.[5,6]

Despite the high frequency of infant colic, its cause remains unclear, and evidence regarding treatment is limited.[7] Several possible etiologic factors have been suggested, including neurodevelopmental and psychosocial factors, altered gut microbiota composition, and lactase deficiency.[7,8] A 2018 Cochrane systematic review assessing several dietary modifications for treating infant colic found that current evidence is insufficient to conclude on the effectiveness of lactase supplementation in managing infant colic.[9] However, additional trials have recently been published.[10,11] The aim of this systematic review was to summarize the evidence on the efficacy and safety of lactase supplementation for the management of infant colic.

What is Known

- Although infant colic is a common problem during the first months of life, there is no well-established treatment.
- Evidence on the use of lactase supplementation in the treatment of infant colic is limited.

What is New

- Three individual studies reported reduced crying duration during lactase treatment, although a meta-analysis of two randomized controlled trials found no difference in crying duration during 1 week of lactase supplementation compared with placebo.
- Lactase treatment was associated with fewer adverse events than placebo.
- The findings of this systematic review may guide further studies and the development of clinical practice guidelines.

2 | METHODS

The protocol of this systematic review registered in PROSPERO (CRD42023441112) and accepted for publication by JPGN Reports. For a summary of the Methods, see Table, Supplemental Digital Content 1.

The preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines[12] for a systematic review and the Cochrane Handbook for Systematic Review of Intervention Version 6.3[13] were followed.

3 | RESULTS

3.1 | Study characteristics

For the process of study selection, see Figure 1. Five full-length papers were included, involving 391 infants[10,11,14–16] Excluded studies, with reasons for exclusion, and one ongoing study are reported in Table, Supplemental Digital Content 2.

The risk of bias for randomized controlled trials (RCTs) is reported in Figure 2. Only one trial was assessed as having a low risk of bias in all domains.[11] The other four studies had methodological limitations in at least one domain, including an unclear randomization process (three RCTs), deviations from intended interventions (two RCTs), missing outcome data (two RCTs), improper measurement of outcomes (two RCTs), and selection of the reported results (four RCTs). The overall risk of bias was assessed as high for three RCTs[10,14,16] and as raising some concern for one RCT.[15] Only one RCT [11] reported registration of protocol and sample size calculation. The characteristics of all included studies are summarized in Table, Supplemental Digital Content 3. The trials were conducted in two European countries (Ireland, United Kingdom), two Asian countries (Indie, Pakistan), and Australia. Two of the five RCTs had two parallel arms[10,11]; while the other three used a cross-over design.[14–16] However, one of the cross-over studies was analyzed as a parallel study.[16] In the cross-over trials reported wash-out periods ranged from 2 days[16] to 5 days[15]; in one study there was no wash-out period.[14] The duration of the interventions lasted from 7 days[14] to 28 days.[11] None of the included trials planned any follow-up after the completion of the intervention. All trials were reported as double-blinded.[10,11,14–16] Two studies included both breast-fed and formula-fed infants.[11,15] One RCT was conducted in exclusively formula-fed infants,[16] while another included only breast-fed infants.[14] In the remaining study, breast-fed and mixed-fed infants were eligible.[10]

Two RCTs[10,11] included infants under 6 months and 5 months, respectively. In two other RCTs, the infants' ages ranged from 3 to 13 weeks[15] and from 3 to 9 weeks[14]; in one trial, the infants' age ranged from 23 to 112 days.[16] Infant colic was diagnosed using Wessel criteria in one study[10] and modified Wessel criteria in two trials.[15,16] The modification of the Wessel criterium meant change in duration of symptoms: 2 weeks duration in first study[15] and any duration in the second study.[16] Another RCT used the Rome IV Criteria to

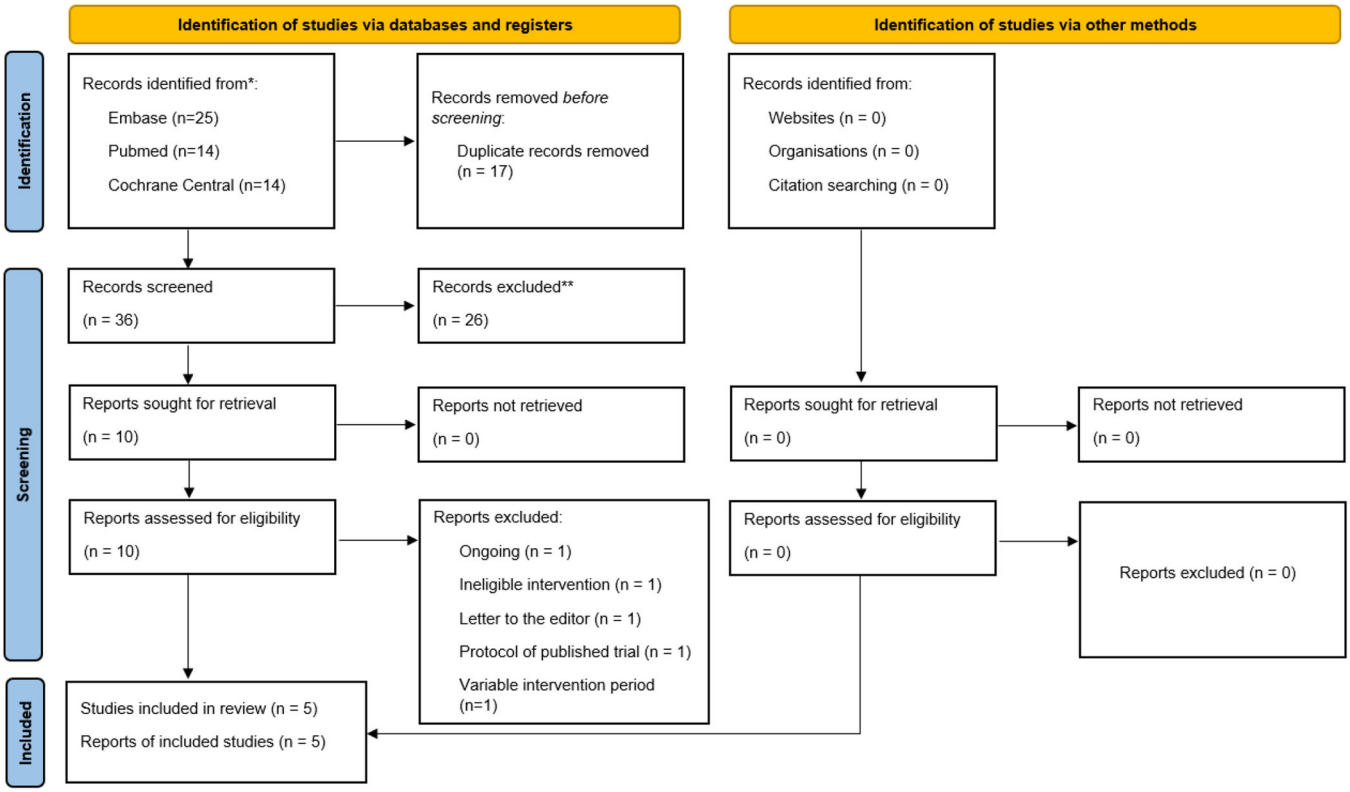


FIGURE 1 PRISMA 2020 flow diagram. Identification process for eligible trials.

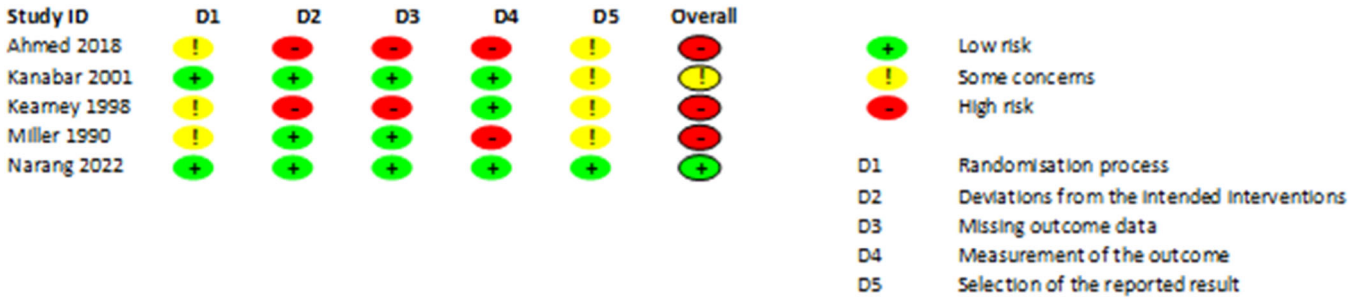


FIGURE 2 Risk of bias in the included studies.

diagnose infant colic,[11] and in one additional study, infant colic was diagnosed based on criteria established by the study authors.[14] In all RCTs, the same dosage of lactase and placebo was used.[10,11,14–16] In all studies, lactase drops were used[10,11,14–16]; however, there were discrepancies between the RCTs regarding the administration and dosage of lactase. In four studies, prior preparation with breast milk or formula was required[10,11,15,16]; in two of those RCTs, the dosage varied depending on the type of feeding.[10,15] In one trial, lactase drops were administered directly into the infant's mouth.[14] Funding was reported by the authors of three out of the five studies.[10,11,15] In the other two studies, no information regarding funding was provided. In one RCT, nonfinancial support was declared.[16] Authors of two RCTs reported no conflict of interest,[10,11] in the other three trials, competing interests were not reported.

3.2 | Summary of findings

3.2.1 | Decrease in daily crying (main outcome)

The main outcome was reported in three RCTs that randomized 214 infants.[10,15,16] In these trials, there was a difference in daily crying duration between the group supplementing lactase and the placebo group. However, the decrease in daily crying was reported differently across the included studies. In one parallel RCT ($n = 104$),[10] a decrease in daily crying was found in the lactase group compared to the placebo group after the first and second weeks of treatment (risk ratio [RR] 0.39, 95% confidence interval [CI], 0.18 to 0.85; number needed to treat [NNT] 4.7, 95% CI 2.7 to 19.1 and RR 0.33, 95% CI, 0.16 to 0.72; NNT 3.7, 95% CI, 2.3 to 9.4, respectively). The decrease in daily crying was defined as a duration of crying below 3 h a day and was measured with a questionnaire during two follow-up visits. In two cross-over RCTs,[15,16] the decrease in daily crying was recorded daily during both the intervention and placebo periods by parents (measured in minutes or hours per day). In the first study,[15] the authors reported a slight decrease in daily crying (22.4%) in the intention-to-treat (ITT) analysis during the 10-day intervention; however, this difference was not significant ($p = 0.09$). In an analysis of only compliant infants, a decrease in daily crying was noted in the lactase group compared to the placebo group (40.4%, $p = 0.0052$). In the second trial,[16] a decrease in mean daily crying time by 1.4 h per day (SE 0.413, 95% CI, 0.23 to 2.05) was found in the lactase group compared with the placebo group during the 7 days of intervention.

3.2.2 | Duration of crying

The duration of crying (measured in minutes per day) during the intervention was reported in four RCTs.[11,14–16] In a meta-analysis of two RCTs (one cross-over and one parallel),[11,14] no difference was found between the lactase and placebo groups in terms of the mean duration of crying (in minutes) for 1 week (MD −17.66, 95% CI, −60.83 to 25.51; $I^2 = 68\%$) (Figure 3). The meta-analysis was feasible for only two trials where the intervention was evaluated either fully or partially after a week. The inclusion of the other studies was hindered by variations in study duration or insufficient data such as standard deviation (SD). In one 4-week parallel study,[11] with 154 participants, the mean duration of crying was shorter in the lactase group compared to the placebo group during the second (MD −40.20 min/day, 95% CI, −62.95 to −17.45), third (MD −52.20, 95% CI, −75.34 to −29.06), and fourth week (MD −50.10, 95% CI, −74.03 to −26.17) of treatment. In one cross-over study[17] with 46 participants, the median duration of crying was reported in both the compliant and ITT analyses. In the lactase group, it was 520.0 and 657.5 min, and in the placebo group, it was 872.5 and 847.5 min during the 10-day intervention, respectively. In another 7-day cross-over study,[16] the mean duration of crying was reported for each group (85.8 min in the intervention group and in 154.2 min the placebo group). However, a difference between the groups was not calculated due to missing SDs.

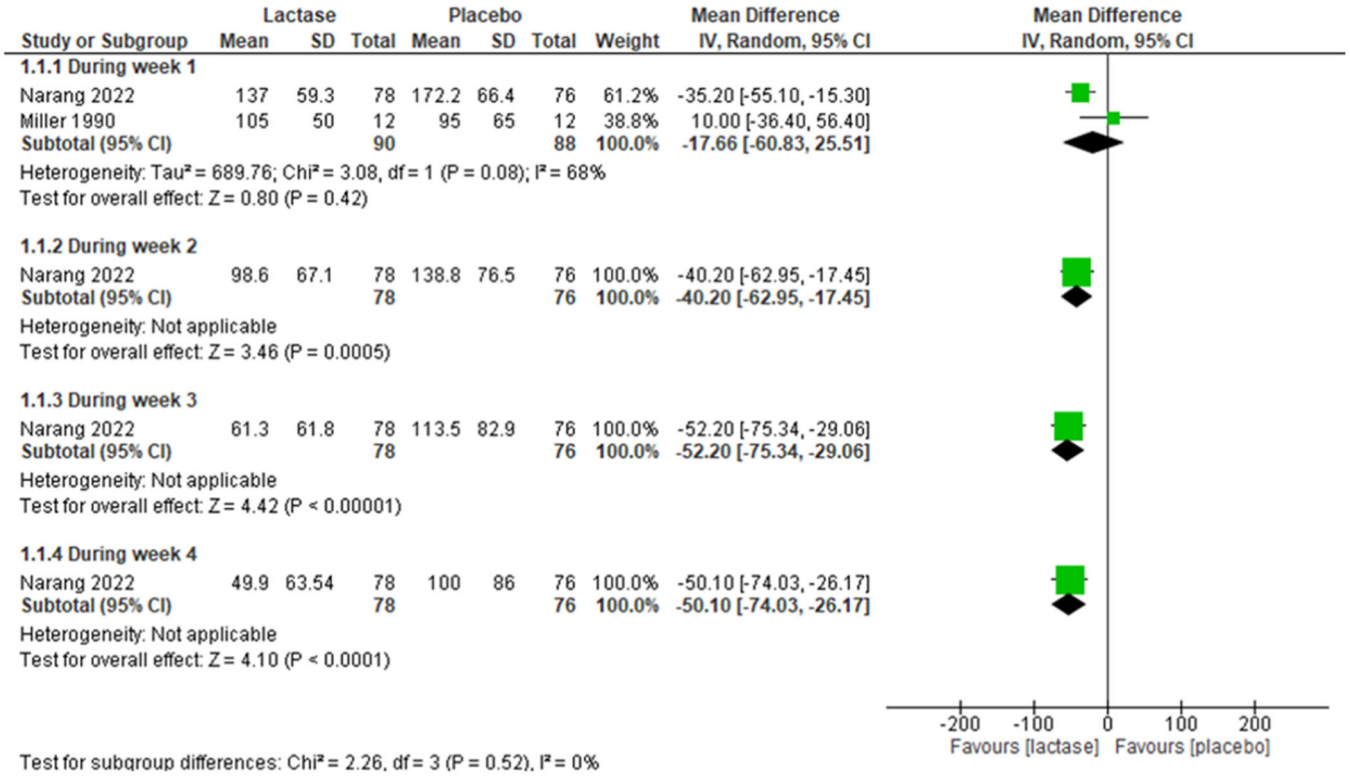


FIGURE 3 Effects of lactase on the duration of mean daily crying compared with placebo.[11,14]

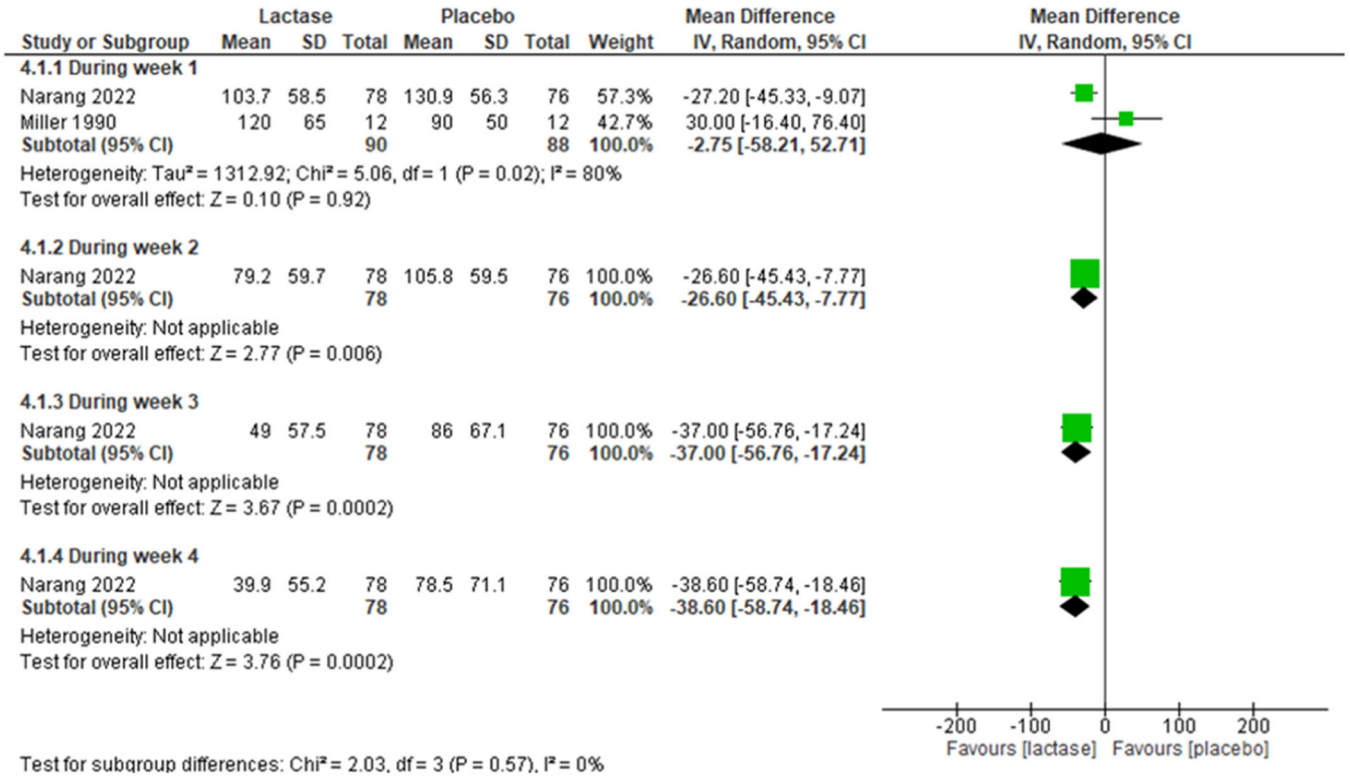


FIGURE 4 Effects of lactase on discomfort of infants (duration of fussing) compared with placebo.[11,14]

3.2.3 | Infant sleep duration

Infant sleep duration was reported in only one crossover RCT with 12 participants.[14] Parents recorded their infants' sleep duration for three consecutive days during both the lactase and placebo periods (Days 14–16 and 21–23). There was no difference in sleep duration between the lactase and control groups during 1 week of treatment (MD –5 min/day, 95% CI, – 107.98 to 98.98).

3.2.4 | Parental satisfaction

Only one 4-week parallel RCT assessed parental satisfaction.[11] Six items (parents' perception of their child's mood, activity, alertness, oral intake, vomiting, and comfort) were measured with the use of a 5-point Likert scale. However, the difference between the groups was not reported; the results were presented only as medians for each item for both the lactase and placebo groups.

3.2.5 | Discomfort of infants

In two RCTs involving 166 participants, the duration of fussing was assessed.[11,14] However, the definition of outcome was not provided in any of the trials. In a meta-analysis of these two studies,[11,14] there was no difference in the mean duration of fussing (measured in minutes) between the lactase and placebo groups during 1 week of intervention (MD 2.75, 95% CI, –58.21 to 57.21; $I^2 = 80\%$) (Figure 4). In one parallel RCT, the mean duration of fussing was shorter in the lactase group compared to the placebo group during the second, third, and fourth weeks of treatment (MD –26.69 min/day, 95% CI, –45.34 to –7.77, $p = 0.006$; MD –37, 95% CI, –56.76 to –17.24, $p = 0.0002$ and MD –38.60, 95% CI, –58.74 to –18.46, $p = 0.0002$).[11]

3.2.6 | Adverse events

Only one parallel RCT reported adverse events.[11] The total number of adverse events was lower in the lactase group than in control group (RR 0.38, 95% CI, 0.21 to 0.68; number needed to harm [NNH] 3.9, 95% CI, 2.6 to 8.5). However, regarding the individual adverse events, only the number of infants with regurgitation of feeds was lower in the lactase group compared to the placebo group (RR 0.27, 95% CI, 0.08 to 0.92; NNH 9.4, 95% CI, 5.1 to 58.7) (Figure, Supplemental Digital Content 4).

3.2.7 | Hospital admissions

Only one parallel trial[11] reported the number of hospital admissions related to adverse events during the intervention. However, no hospitalizations were found in either group.

3.2.8 | Other outcomes

The frequency of crying episodes and family quality of life during the intervention were not reported in any of the included trials.

4 | DISCUSSION

4.1 | Summary of evidence

This systematic review updated the efficacy and safety of lactase supplementation compared to placebo for infant colic, including five RCTs that lasted from 7 to 28 days. The risk of bias was low in one RCT, high in three, and raised some concerns in one. Three RCTs reported reduced crying duration with lactase, although one showed an effect only in a compliant group. A meta-analysis of two RCTs found no difference in crying duration during 1 week of lactase treatment compared to placebo. In two other studies, the difference between groups was not reported. Sleep duration and infant fussing were less frequently reported. One RCT found no difference in sleep duration during a 1-week treatment. Another RCT reported less fussing in the lactase group compared to the placebo group over 3 weeks, but a meta-analysis of two RCTs found no difference during 1 week of lactase supplementation. Other outcomes such as adverse events, hospital admissions, and parental satisfaction were assessed in only one 4-week RCT. It reported fewer adverse events and feed regurgitations in the lactase group compared to the placebo group, with no hospital admissions related to adverse events in either group. Parental satisfaction was reported in only one study but not compared between groups. No RCT reported on the frequency of crying episodes or family quality of life.

4.2 | Agreement and disagreement with other studies

Three previous systematic reviews have assessed the use of lactase supplementation in the management of infant colic.[9,17,18] A 2012 systematic review[17] evaluated pharmacological, nutritional, and behavioral

interventions and identified only two RCTs (58 infants) regarding lactase.[14–16] However, the data were inconclusive in supporting the use of lactase for infants with colic.[17] Another systematic review[18] included 17 studies and focused on common interventions for managing infant colic in breast-fed or mixed-fed infants. It included only one RCT (53 infants) that assessed the use of lactase in infant colic.[15] According to the authors, the risk of bias was low. However, due to poor reporting of findings, there was insufficient evidence for a beneficial effect of lactase in infant colic.

A more recent Cochrane review[9] summarized the effects of various dietary interventions for infant colic and included three RCTs evaluating lactase supplementation (138 infants).[14–16] The risk of bias was assessed as high for all three trials. A meta-analysis was not performed due to high heterogeneity in outcome reporting and limited data. Evidence was insufficient to assess the effects of lactase, although no adverse events were reported in any of the studies. Although the outcomes in the Cochrane review were not based on a core outcome set, the evaluated outcomes were similar to those assumed by this review. Including two new studies in our review added more data about lactase supplementation and its influence on the decrease in daily crying, crying duration, and discomfort of infants. These studies also allowed for the assessment of parental satisfaction and specific adverse events that had previously been omitted. However, none of them evaluated the family's quality of life and the frequency of crying episodes. Similar to previous systematic reviews, the findings of this review remained inconclusive, despite the inclusion of two new studies with larger sample sizes.

4.3 | Strengths and limitations

One of the strengths of this systematic review is its rigorous methodology, which follows the recommendation of the Cochrane Collaboration. The protocol of this review was previously registered. The search strategy was developed with no language or date restriction to ensure completeness of identified RCTs. This review is also the first to use the new Cochrane tool for assessing the risk of bias in trials on lactase supplementation in infants with colic. Additionally, is includes two recently published large RCTs that examine the effects of lactase on infant colic.

For the first time, in line with a 2016 study,[19] we used a standardized core outcomes set to select the outcomes for assessment. This core outcome set includes duration of crying, family stress, infant sleep time, family quality of life, infant discomfort, and hospital admission/duration. However, most of these outcomes were not reported in the included trials, highlighting the need for further large, well-designed RCTs.

On the other hand, some limitations should be considered. The first is the small number of included RCTs. That also made it impossible to perform the planned subgroup analyses based on the type of feeding, infant colic definition criteria, and risk of bias.

Moreover, the methodological quality varied among the trials; only one was methodologically sound and had a previously published protocol and sample size calculation. The limited number of studies and the presence of bias in at least one domain for three out of four RCTs reduces the certainty of the evidence. There were also discrepancies among the included RCTs, such as varying diagnostic criteria of infant colic, and different duration and dosage of lactase. Another limitation is the inconsistent and poor outcome reporting, which made it difficult to compare the findings of different studies. However, whenever feasible, missing difference between groups (MD or RR) was calculated. Adverse events were well reported only in one study.

5 | CONCLUSION

The evidence for the efficacy of lactase supplementation in treating infant colic is currently inconclusive. Individual trials have shown some promise, but the overall quality and consistency of the evidence are lacking. Therefore, there is a clear need for more rigorous, well-designed RCTs that use a standardized core outcomes set for better comparability and reliability.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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