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The Effect of Probiotics Added to Maternal Nutrition on Infantile Colic: A Systematic Review and Meta-analysis

Maternal Beslenmeye Eklenen Probiyotiklerin İnfantil Kolik Üzerine Etkisi: Sistematik Bir İnceleme ve Meta-analiz

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ABSTRACT Objective: This study thoroughly evaluates the available evidence examining the effect of probiotics and derivatives added to maternal nutrition on infantile colic. **Material and Methods:** A comprehensive, systematic search of PubMed, Web of Science, the Cochrane Library, CINAHL and ULAKBİM databases was completed. In the systematic review, we examined the evidence about probiotics that could potentially be included. Contrary to what is usual, our review included maternal nutrition, but not infant feeding. Outcomes data including treatment success and crying times of infantile colic were collected to conduct an analysis. Meta-analysis of study outcomes was performed using Review Manager. The Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) approach was used to assess the quality of the body of evidence for each outcome of this meta-analysis. PROSPERO; registration number CRD42020155237. **Results:** In the review, 4 studies (1,110 participants) were included. The agreement between the 2 researchers was excellent, with Cohen kappa scores [95% confidence interval (CI)]=0.95 (I0.88-1) for article selection and 0.97 (I0.92-1) for bias scoring. The end of the intervention did not find a significant difference in treatment success between the 2 groups [risk ratio (RR) 1.14; 95% CI (0.4, 2.71)]. In a sensitivity analysis using the fixed effect model, we found a significant difference in favor of probiotics [RR 0.92; 95% CI (0.60, 1.42)]. **Conclusion:** Research suggests that the addition of some probiotics in the diet of mothers is reasonable for the treatment of infantile colic. However, more research is needed.

Keywords: Probiotic; prebiotic; infantile colic; maternal nutrition; meta-analysis

ÖZET Amaç: Bu çalışma, anne beslenmesine eklenen probiyotik ve türevlerinin, infantil kolik üzerindeki etkisini inceleyen mevcut kanıtları derinlemesine değerlendirmektedir. **Gereç ve Yöntemler:** PubMed, Web of Science, Cochrane Library, CINAHL ve ULAKBİM veri tabanlarının kapsamlı ve sistematik araştırması tamamlandı. İnfantil kolik tedavi başarısı ve ağlama sürelerini içeren sonuç verileri, analiz yapmak için toplandı. Sistematik incelemede, potansiyel olarak dâhil edilebilecek probiyotiklerle ilgili kanıtları inceledik. Alışılmışın aksine incelememiz, bebek beslemesini değil anne beslenmesini içeriyordu. Çalışma sonuçlarının metaanalizi, "Review Manager" kullanılarak gerçekleştirildi. Tavsiye, Değerlendirme, Geliştirme ve Değerlendirme Çalışma Grubu Dereceleri (GRADE) yaklaşımı, bu metaanalizin her bir sonucunun kanıt kalitesini değerlendirmek için kullanıldı. PROSPERO; kayıt numarası CRD42020155237 idi. **Bulgular:** İncelemeye, 4 çalışma (1.110 katılımcı) dâhil edildi. Makale seçimi için Cohen kappa skorları [%95 güven aralığı (GA)]=0,95 (I0,88-1) ve ön yargı skorlaması için 0,97 (I0,92-1) ile 2 araştırmacı arasındaki uyum mükemmeldi. Müdahalenin sonunda 2 grup arasında tedavi başarısında anlamlı bir fark bulamadık [risk oranı (RO) 1,14; %95 GA (0,4; 2,71)]. Sabit etki modelini kullanan bir duyarlılık analizinde, probiyotikler lehine anlamlı bir fark bulduk [RO 0,92; %95 GA (0,60; 1,42)]. **Sonuç:** Araştırmalar, annelerin diyetine bazı probiyotiklerin eklenmesinin, infantil kolik tedavisi için makul olduğunu göstermektedir. Ancak daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Probiyotik; prebiyotik; infantil kolik; maternal beslenme; meta-analiz

Infantile colic is defined on Wessel's criteria, also known as the 'rule of threes', which as paroxysms of irritability, fussing or crying lasting ≥3 hours per day on ≥3 days per week for >3 weeks".[1] Infantile colic is now a prevalent issue that one in five babies (20%) less than three months old has been facing.[2]

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Although infantile colic is considered a self-limiting and benign problem, it is a stressful problem for both newborns and parents.[3-5] Infantile colic may cause health problems in the short and long term for newborns, it is also associated with poor quality of life for parents and negatively affects the social and psychological state.[6,7]

There is no clear line regarding infantile colic etiology. However, it is thought that there may be the mode of delivery, the feeding style of the newborn, birth weight, lactose intolerance, intestinal contractions, gas food hypersensitivity, parental misinterpretation of the normal crying model, or various combinations of these.[3,8,9] Efficiency of applying manipulative therapies, probiotics, dietary modification, complementary and alternative therapies (herbal formulations, sucrose or glucose) and pain-relieving agents have been heretofore analyzed and evaluated.[10,11] Recent research and related evidence suggest that motility impairment and intestinal neuronal hyperexcitability are the most important pathogenic factor in infantile colic etiology.[12-15] There is growing evidence that intestinal microbiota differs from healthy controls in infants with colic. It is also evident that a large number of aerobic bacteria e.g. *Helicobacter pylori* was detected in the microbiota of infants having colicky symptoms such as excessive crying or irritability, nonetheless, microbiota of infants who are not diagnosed as colic are more diverse than the former.

Use of probiotics and prebiotics in alleviating and curing colic symptoms as well as other related problems e.g. functional intestinal disorders has been searched in numerous studies in order to make accurate conclusions.[16,17] Microbiota is believed to be changed or modified by some factors and this alteration in microbiota may trigger the colic suffering in babies. Hence, prophylactic use of probiotics may relieve the colic pain by ensuring the balance of microbial bowel colonization. However, it should not be forgotten that the colic does not have a single reason, its etiology is multifactorial and although many treatments are available for infantile colic, there is no universally effective and acceptable treatment.[18] Hence, additional approaches to treatment can be valuable. Probiotics are an increasingly popular treatment intervention that is particularly popular with infantile colic therapy.[19,20] Numerous studies have shown that the use of probiotics in the treatment of infantile colic is promising and there is evidence for the efficacy of probiotics in infant feeding for infantile colic.[21-23] However, there is a lack of evidence for the efficacy of probiotics added to maternal nutrition, and there is no guidance available to clinicians or the community.[24] Therefore, it is important to evaluate whether probiotics added to maternal nutrition are effective as primary or preventive treatment for newborn colic.[25]

The aim of this study is to figure out the efficiency and safety of pro-prebiotics added to maternal nutrition in preventing or reducing severity of infantile colic.

MATERIAL AND METHODS

Systematic review and meta-analysis of studies determining the effect of safety of probiotics, prebiotics or synbiotics (PPS) added to the diet of mothers on infantile colic were performed. The study was prepared in accordance with the recommendations in the "Systematic Reviews Handbook of Cochrane Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis".

SEARCH STRATEGY

The systematic literature review of this study was registered with the "International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020155237)." A comprehensive, systematic search of PubMed, Web of Science, the Cochrane Library, CINAHL, ULAKBİM databases was completed from the earliest date available until January 2020. The main key word and MESH headings used in this study are as follows: '(Colic or infantile colic or excessive crying) and (probiotics or prebiotics or synbiotics) and (pregnancy or postpartum) and (maternal nutrition or maternal diet). The search strategy was modified according to the specifications of each database. Moreover, the reference lists of retrieved articles were reviewed to identify further undiscovered relevant articles. The detailed information is shown in Figure 1.

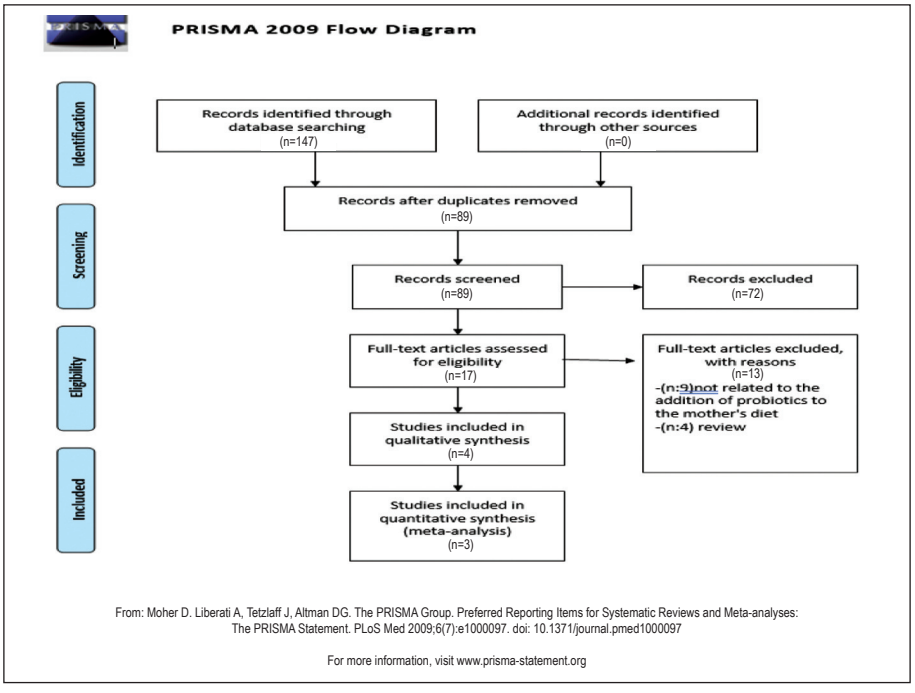

FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) diagram.

INCLUSION AND EXCLUSION CRITERIA

Studies were included if they met the following criteria: (1) Observational study designs (cohort, case-control, cross-sectional) and randomized controlled trials (RCTs), (2) Studies published only in English and Turkish languages were included, (3) Prophylactic, PPS (any dose or composition) added to the mother's diet during pregnancy or postpartum period, (4) Healthy pregnant women over 36 weeks of gestation in studies, (5) Mothers who breastfeed their baby predominantly -more than 50% of baby's daily diet.

Studies were excluded in the light of the following criteria: (1) Those who use PPSs before the thirty-sixth gestational week, (2) Receive alternative therapies (massage, nutritional diets, etc.) other than PPSs for colic treatment, (3) Babies who are fed with formula only or more than 50% of their daily diet, (4) Preterm or low birth weight babies, (5) Mothers who used antibiotics during pregnancy or postpartum period were not included in the review.

STUDY SELECTION AND DATA EXTRACTION

After the duplicate articles retrieved from the different databases were removed, 2 independent investigators (A.Y.K., G.D.) screened titles and abstracts to identify which studies met the inclusion and exclusion criteria. Studies that were fulfilled by the inclusion criteria or those with eligibility that could not be identified from the title/abstract screening were retrieved for full-text and review by 2 investigators (A.Y.K., G.D.). Disagreements between reviewers were resolved by consulting with a third reviewer (M.Ö.) who was blind to other reviewers' decisions on inclusion.

Two investigators independently extracted the following data: Characteristics of participants, interventions and controls, methods, outcomes. When the data of the articles were insufficient or uncertain, one of the authors (A.Y.K.) contacted the first author to request detailed information about the research via e-mail. The quality of the selected articles was assessed by The Effective Public Health Practice Project (EPHPP) checklist, which is a quality assessment tool for quantitative studies.

ASSESSMENT OF RISK OF BIAS

Two investigators (A.Y.K. and G.D.) independently assessed the study for risk of bias, using the criteria recommended in the Cochrane Handbook for Systematic Reviews of Interventions: sequence generation; allocation concealment; blinding of parents and

health professionals; blinding of outcome assessment; incomplete outcome data; selective outcome reporting and other potential threats to validity. We judged each domain as being at low, high or unclear risk of bias. We compared the judgements and discussed and resolved any inconsistencies in the assessments. A third investigator (M.Ö.) made a final decision if consensus was not reached by the first two investigators.

QUANTITATIVE DATA SYNTHESIS AND ANALYSIS

Outcomes data including treatment success and crying times of infantile colic were collected to do an analysis. Meta-analysis of study outcomes was performed using RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). The Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) approach was used to assess the quality of the body of evidence for each outcome of this meta-analysis. The quality of evidence was initially considered "High" and could be downgraded based on the following 5 factors: 1) limitation of design, 2) indirectness of evidence, 3) inconsistency of results, 4) imprecision of results, and 5) high probability of publication bias.

Pooled values were calculated as the inverse variance-weighted mean of the logarithm of risk ratio (RR) with 95% confidence intervals (CI) to assess the strength of association between probiotics and treatment success. For analysis of continuous data, mean differences (MD) or standardized MD with 95% CI were used. If all studies report the outcome, using the same scale such as Barr Baby Diary Scale for treatment success MD was used. The follow-up time of the included studies differs from 7 days 30 to 1 year. In this meta-analysis, all of them were accepted.

The random-effects model was used to account for variability between studies and its effect on the intervention. The I^2 statistic was used to measure the heterogeneity between included studies and the I^2 value of 25% which indicates a small, 50% a moderate, and 75% a high degree of heterogeneity. Coherence between researchers for independent article selection and bias scores was evaluated using the Cohen kappa statistic. Effect size was excepted 0.2 as small, 0.5 as moderate, and 0.8 as large using Cohen's criteria for pooled estimates.

RESULTS

The electronic database search and hand-search yielded 147 potentially relevant studies. After removing duplicates, we screened 89 articles based on title or abstract. The remaining 17 full texts were assessed for the eligibility. For the full-text screening, a third reviewer was needed to resolve disagreements for blinding of the studies. Four trials met all eligibility criteria and were included in qualitative synthesis (Figure 1). Only 50% (n=2) of the studies graded 1 according to EPHPP tool.[24] Coherence between the observers was excellent both in the selection of articles and in the scoring of selected articles in terms of bias Cohen kappa (95% CI)=0.95 (I0.88-1) for article selection, 0.97 (I0.92-1) for bias scoring.

The quality of evidence included in this meta-analysis was assessed using the GRADE approach. Treatment success and crying times were the outcomes assessed. The results regarding the outcomes showed low to moderate evidence. The GRADE analysis can be seen on Table 1.

THE CHARACTERISTICS OF INCLUDED STUDIES AND POPULATION

Three RCTs and a single interventional study, including 1,036 mothers and babies, were included in our systematic review and 3 RCTs were included in the meta-analysis.[26-29] The characteristics of the studies are summarized in Table 2. With one exception, all trials are double-blind and placebo-controlled.[28] All articles included in the study were published in English. All of the mothers included in the study reported that they breastfed their babies (>50%). In a single study, its design started in the prenatal period (36th gestational week) by adding probiotics and continued until the first month after birth.[27] In a single RCT prenatal period (36th gestational week) was started by adding synbiotics to mother feeding and continued until the first month after delivery.[26] In newborns diagnosed with postpartum colic in a single interventional and a single RCT made by Iacovou, it started to work by adding a prebiotic diet to the mother diet and continued for 7-10 days.[28,29]

TABLE 1: Grade analysis and sum of findings.

Summary of findings:

Probiotics compared to placebo for infantile colic for infantile colic

Patient or population: infantile colic
Setting:
Intervention: probiotics
Comparison: placebo for infantile colic

Outcomes	Anticipated absolute effects* (95% CI) Risk with placebo for infantile colic	Risk with probiotics	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
crying times assessed with: minutes per day follow up: median at study end	The mean crying times ranged from **from across control groups from 66 minutes per day to** 52 minutes per day	MD **50 52 minutes per day lower** (168.73 lower to 68.73 higher)	-	13 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	
treatment success assessed with: Wessel\Rome III criteria follow up: median at study end>%50 decrease crying times days	67 per 1.000	**76 per 1.000** (32 to 181)	**RR 1.14** (0.48 to 2.71)	1098 (3 RCTs)	⊕⊕◯◯ LOW [b,c]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. total population<300
b. high heterojenity >72I²
c. the tree studies did not indicate result of the colic search in the trial record

The duration of the interventions ranges from 10 days to six month.[27,28]

One study used synbiotic instead of probiotics, and prebiotic diet instead of probiotics.[27-29]

THE CHARACTERISTICS OF THE ADDED INTERVENTION

Among the articles included in the study, Baldassarre et al., a probiotic preparation containing different probiotic strains (*Lactobacillus paracasei* DSM 24733, *Lactobacillus plantarum* DSM 24730, *Lactobacillus acidophilus* DSM 24735 and *Lactobacillus delbruecki*), Iacovou et al. study, a prebiotics diet-FOPMAP (Prebiotic diet-fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols) and the Kukkonen et al.'s study, a synbiotic preparation containing different probiotic strains (*Lactobacillus rhamnosus GG* and *L. rhamnosus LC705, Bifidobacterium breve Bb99*, and *Propionibacterium freudenreichii* ssp *shermanii*) were used.[26-28]

CONTROL GROUP

While two studies used placebo as a control group, in a study evaluating its effectiveness against the Australian diet, a group that was diagnosed with colic in the daily diet in an interventional study was later assigned to the probiotic group and its effectiveness was evaluated (Table 2).[26-29]

The duration of the addition of pro-prebiotics to maternal nutrition began in 3 studies at 36 weeks of gestation and continued in the postpartum period. This period ranged from 2 to 6 months.[26,27] In two studies, pro-prebiotics were added to the maternal diet 7 days after the diagnosis of colic and continued to be given for 7-10 days. The dosage schedule and the way of administration of pro-probiotics varied significantly between RCTs.

In any of the studies included, no adverse side effects were reported in the mother or newborn for the supplement added to the mother's diet.

EFFECTS OF INTERVENTIONS

Primary Outcomes

Treatment success at the end of intervention

Except for an interventional study, three articles reported results of treatment success at the end of the intervention, and we performed random effect meta-

TABLE 2: Characteristics of studies included in the systematic reviews and meta-analysis.

First authors, time, country	Study design	Population	Inclusion criteria Exclusion criteria	Intervention (dose/duration of intervention)	Comparison	Follow-up time	Withdrawal number and reason	Primary outcomes Secondary outcomes
Iacovou, 2018, Australia	RCT	13 mothers 1-Prebiotic diet (FODMAP diet): (N: 6) 2-Control Group (Australian diet): (N: 7)	Inclusion criteria -Mothers with a baby younger than 9 weeks -Diagnosed as colic according to Wessel criteria -Mothers between the ages of 18-45 and who want to change their diet -Mothers who are breastfeeding their baby only or predominantly Exclusion Criteria -If there is any underlying medical condition or mother-infant pairs requiring medication were excluded.	FODMAP diet (Fermentable, oligosaccharides, disaccharides, monosaccharides and polyols) The response group was given a 10-day FODMAP diet.	Typical Australian diet	Control after the diagnosis of infantile colic (at the beginning) and on the 10th day	Intervention group (N: 1) Control Group (N: 0)	Primary outcomes: at the end of each diet intervention was the change in combined infant crying and restlessness time (on average 8-10 days).Secondary outcomes include infant feeding, sleep time and wakefulness and periods of content, maternal health (anxiety, depression and stress), and measured fecal and breast milk indices.
Iacovou, 2017, Australia	Interventional	18 mothers	Inclusion criteria -Mothers with a baby younger than 9 weeks -Diagnosed as colic according to Wessel criteria -Mothers between the ages of 18-45 and who want to change their diet -Mothers who are breastfeeding only or predominantly -Term born and-not exposed to any treatment for colic (such as simethicone and wind drops) or anti-reflux medicine Exclusion Criteria -A common disease condition requiring medication, the current use of dietary restriction in response to a baby with colic, and-followed the vegan diet.	FODMAP diet (Fermentable, oligosaccharides, disaccharides, monosaccharides and polyols) A 7-day FODMAP diet was given.	Their diets	After diagnosis of infantile colic (at the beginning) and at the end of the 7-day diet intervention		Primary outcomes: at the end of each diet intervention was the change in combined infant crying and restlessness time (on average 8-10 days).Secondary outcomes include infant feeding, sleep time and wakefulness and periods of content, maternal health (anxiety, depression and stress), and measured fecal and breast milk indices.

TABLE 2: Characteristics of studies included in the systematic reviews and meta-analysis *(continue).*

First authors, time, country	Study design	Population	Inclusion criteria Exclusion criteria	Intervention (dose/duration of intervention)	Comparison	Follow-up time	Withdrawal number and reason	Primary outcomes Secondary outcomes
Baldassarre, 2016, Italy	RCT	66 pregnant women 1-Intervention Group 1 (Probiotic): (n: 33) 2-Control Group (Placebo): (n: 33)	Inclusion criteria-Healthy, pregnant women with low obstetric risk Exclusion Criteria -Pre-existing clinical conditions such as diabetes, hypertension, diabetes; hypertension; Autoimmune disease; asthma; allergy; kidney or liver diseases; viral, bacterial or protozoan infection; anemia; twin pregnancies; pregnancy disease and preterm births; smoking more than 10 cigarettes per day; Use of other probiotics during the study protocol	Intervention (n=33: 30 breastfeeding and 3 mix feeding): high concentration, multi-strain probiotic supplement, in packs. 4 different lactobacilli strains (Lactobacillus paracasei DSM 24733, Lactobacillus plantarum DSM 24730, Lactobacillus acidophilus DSM 24735 and Lactobacillus delbrueckii subsp bulgaricus DSM 24734), 3 strain bifidobacteria (Bifidobacterium longum DSM 24736, Bifidobacterium breve DSM 24734) 900 billion viable lyophilized bacteria 24737) and 1 Streptococcus thermophilus DSM 24731 strain.	Control (n=34: 29 breastfeeding and 5 mixture feeding; 1 of them could not follow): corn starch	Postpartum Day 0 and Day 30	Experiment Group (N: 0) Control Group (N: 1)	Primary outcomes analysis of breast milk for cytokine patterns, secretion in breast milk and feces IgA, fecal lactoferrinSecondary outcomes: safety, anthropometric data and gastrointestinal events (insufficiency, bowel movements and colic symptoms in the newborn or toddler period according to Rome III criteria)
Kukkonen, 2008, Helsinki, Finland	RCT	939 pregnant women 1-Response Group (Synbiotic) (n=468): 2-Control Group (Placebo) (n=471):	Inclusion criteria -Pregnant women with children at high risk of allergies from antenatal clinics Exclusion Criteria <37 weeks gestational age, twin baby, major malformation	Intervention (n=468): Received capsules containing a pregnant mixture of 36 weeks Lactobacillus rhamnosus GG and C705, Bifidobacterium breve LBb99 and Propiobibacterium freudenreichii ssp shermanii JS (8-9 x 10 9, CFU in each capsule). For 6 months after birth, babies were given 1 open capsule of the same probiotics and 0.8 g of GOS in liquid form daily. 4 weeks before birth and 6 months after birth.	0.8 g GOS (bovine origin) was given in placebo (microcrystalline cellulose plus sugar syrup).	Timing of measurements: 3, 6, 12 and 24 months	Not reported, but 939 participants completed the 6-month follow-up and 925 participants completed the 2-year follow-up baby only or predominantly	Primary outcomes: neonatal morbidity, infantile colic and defecation, nutritional behaviors (vomiting, constipation, excessive crying and abdominal discomfort) Secondary outcomes: anthropometric measurement, infection, antibiotics and other diseases.

RCT: Randomized controlled trial; Ig: Immunoglobulin; CFU: Colony-forming unit; GOS: Galacto-oligosaccharide.

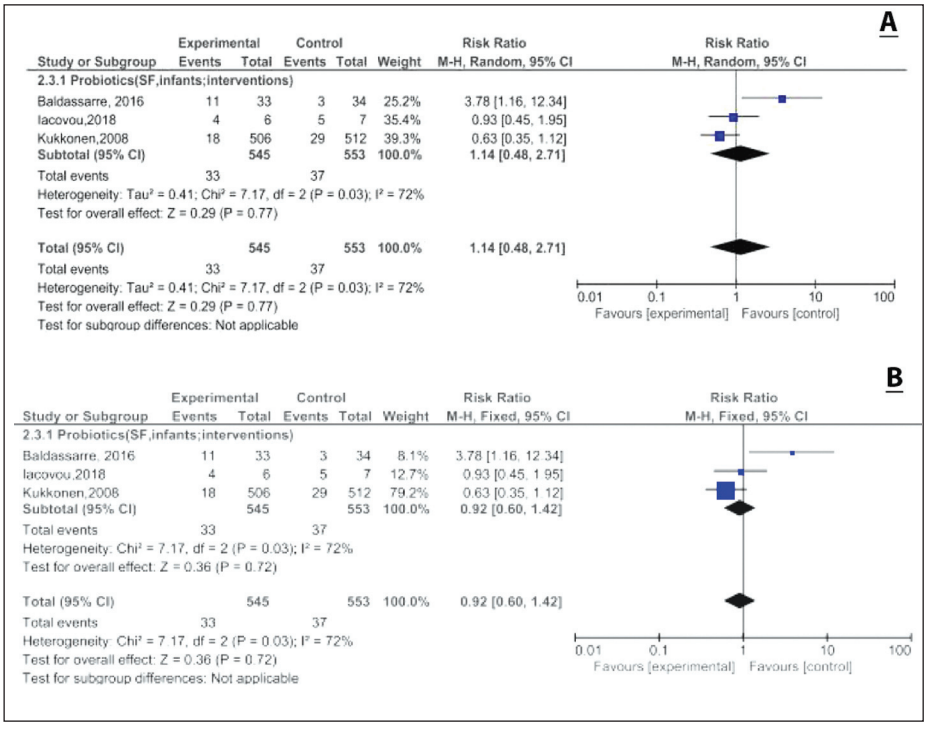

FIGURE 2: A) Forest plot of comparison: 1 Probiotic preparation versus placebo, outcome: 1.1 effect of infantile colic on treatment success at the end of the intervention: random-effects model. **B)** Forest comparison chart: Placebo versus probiotic preparation, effect of infantile colic on treatment success at the end of 1.2 interventions: sensitivity analysis with fixed effect model.

analysis of three studies with 1,097 participants and we did not find a significant difference in terms of treatment success between the two groups (Figure 2A).[26-29] In a sensitivity analysis using the fixed effect model, we found a significant difference in favor of probiotics (Figure 2B).[26] This inconsistency between the two models suggests statistical heterogeneity, and is consistent with the I^2 statistic, which was high at 72%. The quality of the evidence in function was downgraded to moderate quality due to inconsistency.

Secondary Outcomes

Duration of crying at the end of intervention

The combined results of an RCT reported that the application of the probiotic compared to placebo reduced the crying time at the end of the intervention.[26] However, there was no notification of crying time. There was no significant difference in daily crying time between the placebo group at the end of the intervention, but compared with a RCT, a synbiotic application including *L. rhamnosus LC705, B. breve Bb99 and P. freudenreichii* ssp *shermanii JS* did not significantly decrease the crying time.[26]

According to these results, four articles reported results about reduced crying time, but they did not report in minutes. We conducted a random-effects meta-analysis of one study with 13 participants, and found a difference between the two groups in favour of prebiotics for crying time (Figure 3A).[28] In a sensitivity analysis using the fixed effect model, we didn't find a significant difference in favor of probiotics (Figure 3B). The quality of the evidence in function was downgraded to low quality due to imprecision and indirectness. In a single RCT, one interventional study, researchers measured the intervention effect and crying time based on parent reports using a validated Barr Diary (a Baby Day Diary) and a stopwatch for timing infant behavior patterns.[28,29] Another 1 RCT was measured using the structured diary and Bristol Stool Form Scale for gastrointestinal events to evaluate the crying times and the daily state of the baby, based on parent reports.[26] In a single RCT a daily form created by researchers was used.[27] In this study,

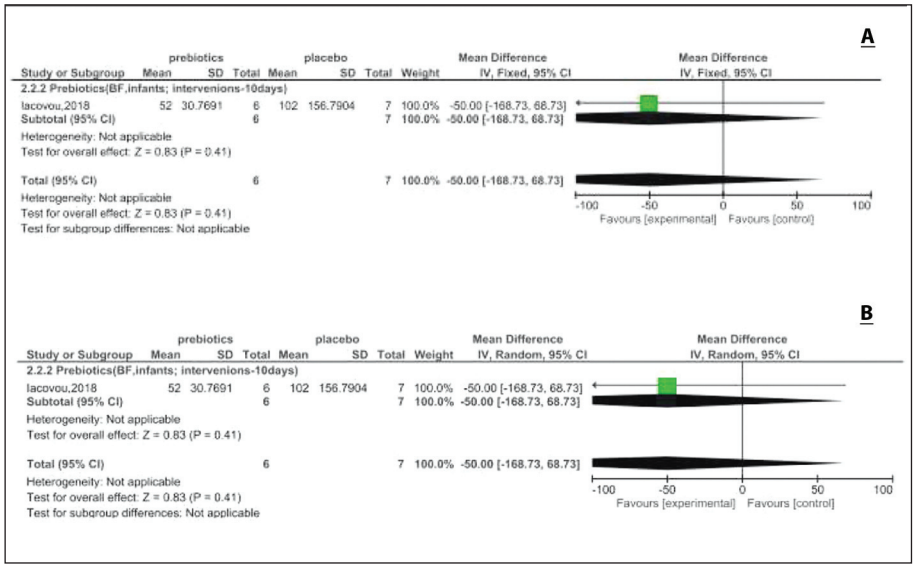

FIGURE 3: A) Forest plot of comparison: 1 Probiotic preparation versus placebo, outcome: Crying time: random□effects model (minutes/day). **B)** Forest comparison table: Probiotic preparation versus placebo, outcome: Crying time: sensitivity analysis with fixed effect model.

the intervention effect and crying time were measured based on parental contextten reports.

RISK OF BIAS ASSESSMENT

The conclusions of our 'bias risk' evaluation for the included studies are summarized in Figure 4 and Figure 5.

Random sequence generation Except for an interventional study, five studies defined an adequate method of random allocation of participants to intervention groups, so we graduated these studies at low risk of bias on this field.[26-29]

Allocation concealment In the studies of Kukkonen et al. and Iacovou et al.; it did not define or mention the hiding of the allocation, so we considered it as a study with an uncertain bias risk. In other two studies, allocation hiding was identified and considered a low risk of bias.[26,28]

Blinding All studies, except the Iacovou et al.'s study (single blind), were double-blind. Three studies were graded with risk of performance bias and detection bias, as they did not describe adequate methods for blinding.[26-28]

Incomplete outcome data Three studies were evaluated with a low risk of wear bias because there was similar or very little dropout rates between the control and experimental groups.[26-28] We decided that the work of Iacovou is at risk of uncertain wear, since its design does not have a control group and uses every mother as its own control.

Selective reporting The two studies were considered a low risk of selection bias, as they discussed all outcomes, including negative outcomes, and reported them in their protocols.[28,29] Two studies carried a high risk in terms of trial registration and reporting bias.[26,27]

Other potential sources of bias As other biases in the study, we have taken into account any involvement of companies supplying or producing the intervention product while conducting the studies or the article, due to the use of a product or intervention in such a vulnerable and risky population. We rated the four studies included in the meta-analysis as having low risk of further bias because they declared that they had no financial relationship with either product support, direct financial support for the business, or no financial relationship with the industry.[26-29]

DISCUSSION

We present the first systematic review of studies dealing with the effect of probiotics added to maternal nutrition in infantile colic. The purpose of this review

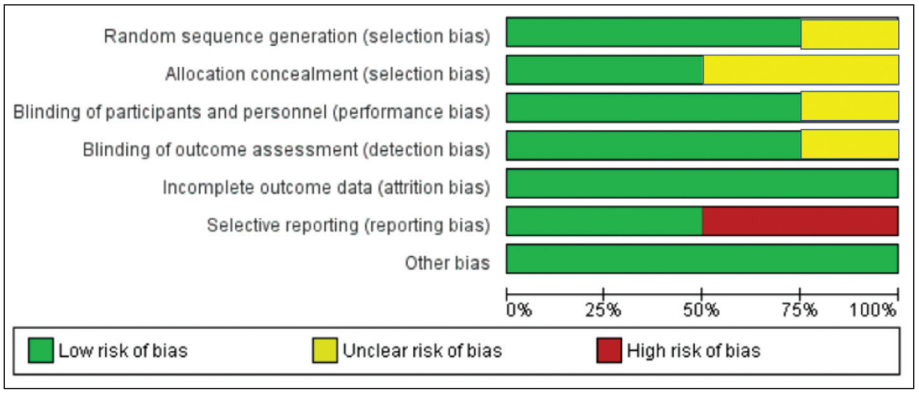

FIGURE 4: Bias risk chart in included trials.

was to summarize available proof on the effectiveness of the probiotic supplement given in the prenatal or postnatal period in infantile colic treatment. We focused on two main outcomes only, these were the success of treatment and the duration of crying time per day, as being clinically important. Both outcomes were assessed at the end of the intervention period.

In the literature, there is no systematic review evaluating the effect of probiotics added to maternal nutrition on infantile colic. The extensive and systematic literature search is one of the strengths of this systematic review. Apart from that, we included only probiotic or prebiotic supplements added to the maternal diet. methodological quality (GRADE) of the included studies was average and low, so we are not sure of the effects of the probiotic supplement on crying time, while it has positive results for treatment success.[25] In this review, 3 RCTs available in the literature were conducted on 1 interventional study. Some of the included studies were limited to the study population as well as probiotic and prebiotic supplements. For example, the effect of the probiotic supplementary used in the study of Baldassarre et al. was mainly studied in breast-fed infants; data on formula-fed infants are restricted and do not encourage formula-fed babies.[27] Moreover, prevalence of infantile colic is similar in breastfed and formula-fed infants. Thus, the generalizability of the findings should not be limited. One important limitation of the included studies was the lack of an objective way to assess the duration of crying in infants. In the interventional study of a single RCT, the researchers measured the intervention effect and crying time

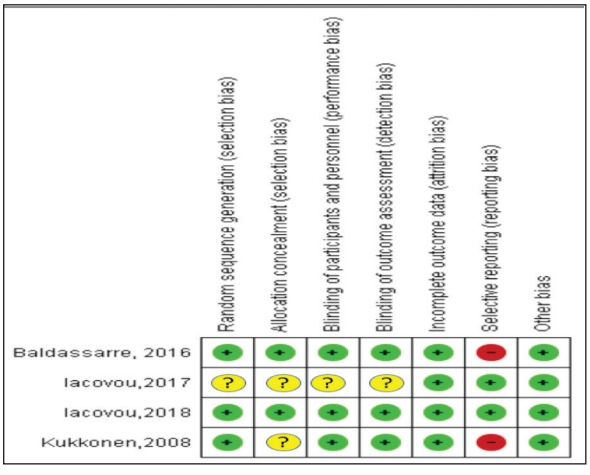

FIGURE 5: Assessment of risk of bias.

based on parent reports, using a validated Barr Diary (a Baby Day Diary) and a stopwatch for timing infant behavior patterns.[28,29] Another 1 RCT was measured using the structured diary and Bristol Stool Form Scale for gastrointestinal events to evaluate the crying times and the daily state of the baby, based on parent reports.[26] In one RCT, a daily form created by researchers was used. In this study, the intervention effect and crying time were measured based on parental reports, but no clear information about the duration was obtained.[27]

The previous systematic reviews were made to evaluate the effects of probiotic applications on crying time in infants with infantile colic when added to infant feeding. These studies did not include maternal nutrition, but our current findings are consistent with the results of previously published reviews.[30,31] How-

ever, the absence of a systematic review focusing only on maternal nutrition causes a situation where the study remains strong but controversial. In addition, as a result of the search criteria valid for the study, very few RCTs were reached, which included only mothers. Apart from that, compared to the probiotics available in the literature, this review included both probiotics and prebiotics.[24,32] Therefore, our analysis defines looking at the role of probiotics and prebiotics in infantile colic treatment according to different treatment options. Anabrees et al. focused on interventions in nursing babies and concluded that probiotics, especially *Lactobacillus reuteri*, seem to be effective in reducing colic, although there are limitations in these findings.[33] In the study of Dryl and Szajewska, which included seven RCTs (471 participants), the application of *L. reuteri* DSM 17938 was associated with less cure time at the end of the treatment compared to placebo; however, the effect was found to be mainly in infants who were breastfed only.[34]

CONCLUSION

In conclusion, this systematic review confirms that the application of probiotics or prebiotics added to maternal nutrition may be beneficial in infants with infantile colic.

Further studies are needed, especially for probiotics and prebiotic supplements added to maternal nutrition. Studies evaluating the effectiveness of some probiotics and/or prebiotics are needed because some preliminary results are quite promising.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Aysun Yıldız Karaahmet, Gülümser Dolgun, Metehan Özen;* ***Design:*** *Aysun Yıldız Karaahmet, Gülümser Dolgun, Metehan Özen;* ***Control/Supervision:*** *Gülümser Dolgun, Metehan Özen;* ***Data Collection and/or Processing:*** *Aysun Yıldız Karaahmet, Gülümser Dolgun;* ***Analysis and/or Interpretation:*** *Aysun Yıldız Karaahmet, Gülümser Dolgun, Metehan Özen;* ***Literature Review:*** *Aysun Yıldız Karaahmet, Gülümser Dolgun;* ***Writing the Article:*** *Aysun Yıldız Karaahmet, Gülümser Dolgun;* ***Critical Review:*** *ysun Yıldız Karaahmet, Gülümser Dolgun, Metehan Özen.*

REFERENCES

1. Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. Pediatrics. 1954;14(5): 421-35. [Pubmed]
2. Bennett WE Jr. Probiotics and infant colic. BMJ. 2014;348:g2286. [Crossref] [Pubmed]
3. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2006;130(5):1519-26. [Crossref] [Pubmed]
4. Steutel NF, Benninga MA, Langendam MW, de Kruijff I, Tabbers MM. Reporting outcome measures in trials of infant colic. J Pediatr Gastroenterol Nutr. 2014;59(3):341-6. [Crossref] [Pubmed]
5. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Çokura F, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. J Pediatr Gastroenterol Nutr. 2015;61(5):531-7. Erratum in: J Pediatr Gastroenterol Nutr. 2016;62(3):516. [Crossref] [Pubmed] [PMC]
6. Drug and Therapeutics Bulletin. Management of infantile colic. BMJ. 2013;347:f4102. [Crossref] [Pubmed]
7. Sung V, Collett S, de Gooyer T, Hiscock H, Tang M, Wake M. Probiotics to prevent or treat excessive infant crying: systematic review and meta-analysis. JAMA Pediatr. 2013;167(12): 1150-7. [Crossref] [Pubmed]
8. de Weerth C, Fuentes S, Puylaert P, de Vos WM. Intestinal microbiota of infants with colic: development and specific signatures. Pediatrics. 2013;131(2):e550-8. [Crossref] [Pubmed]
9. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506-14. [Crossref] [Pubmed]
10. Savino F, Cordisco L, Tarasco V, Locatelli E, Di Gioia D, Oggero R, et al. Antagonistic effect of Lactobacillus strains against gas-producing coliforms isolated from colicky infants. BMC Microbiol. 2011;11:157. [Crossref] [Pubmed] [PMC]
11. Penna FJ, Péret LA, Vieira LQ, Nicoli JR. Probiotics and mucosal barrier in children. Curr Opin Clin Nutr Metab Care. 2008;11(5):640-4. [Crossref] [Pubmed]

12. Liu Y, Fatheree NY, Mangalat N, Rhoads JM. Human-derived probiotic Lactobacillus reuteri strains differentially reduce intestinal inflammation. Am J Physiol Gastrointest Liver Physiol. 2010;299(5):G1087-96. [Crossref] [Pubmed] [PMC]
13. Sung V, Hiscock H, Tang M, Mensah FK, Heine RG, Stock A, et al. Probiotics to improve outcomes of colic in the community: protocol for the Baby Biotics randomised controlled trial. BMC Pediatr. 2012;12:135. [Crossref] [Pubmed] [PMC]
14. Praveen V, Praveen S, Deshpande G, Patole SK. Oral probiotics for infantile colic. Cochrane Database Syst Rev. 2014;3. [Crossref]
15. Savino F, Ceratto S, De Marco A, Cordero di Montezemolo L. Looking for new treatments of Infantile Colic. Ital J Pediatr. 2014; 40:53. [Crossref] [Pubmed] [PMC]
16. Sung V, Hiscock H, Tang ML, Mensah FK, Nation ML, Satzke C, et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. BMJ. 2014;348:g2107. [Crossref] [Pubmed] [PMC]
17. Turner TL, Palamountain S (author), Augustyn M (section editor), Torchia MM (deputy editor). Infantile Colic: Management and outcome. UpToDate 2014. Cited 5 January 2019. [Link]
18. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016: S0016-5085(16)00182-7. [Pubmed]
19. Talachian E, Bidari A, Rezaie MH. Incidence and risk factors for infantile colic in Iranian infants. World J Gastroenterol. 2008;14(29): 4662-6. [Crossref] [Pubmed] [PMC]
20. Savino F, Cordisco L, Tarasco V, Calabrese R, Palumeri E, Matteuzzi D. Molecular identification of coliform bacteria from colicky breastfed infants. Acta Paediatr. 2009;98(10):1582-8. [Crossref] [Pubmed]
21. Biagi E, Nylund L, Candela M, Ostan R, Bucci L, Pini E, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One. 2010;5(5):e10667. Erratum in: PLoS One. 2010;5(6). [Crossref] [Pubmed] [PMC]
22. Ali AM. Helicobacter pylori and infantile colic. Arch Pediatr Adolesc Med. 2012;166(7):648-50. [Crossref] [Pubmed]
23. Newburg DS, Walker WA. Protection of the neonate by the innate immune system of developing gut and of human milk. Pediatr Res. 2007;61(1):2-8. [Crossref] [Pubmed]
24. Gutiérrez-Castrellón P, Indrio F, Bolio-Galvis A, Jiménez-Gutiérrez C, Jimenez-Escobar I, López-Velázquez G. Efficacy of Lactobacillus reuteri DSM 17938 for infantile colic: Systematic review with network meta-analysis. Medicine (Baltimore). 2017;96(51):e9375. Erratum in: Medicine (Baltimore). 2018;97(4):e9730. [Crossref] [Pubmed] [PMC]
25. Rautava S. Early microbial contact, the breast milk microbiome and child health. J Dev Orig Health Dis. 2016;7(1):5-14. [Crossref] [Pubmed]
26. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. Pediatrics. 2008;122(1):8-12. [Crossref] [Pubmed]
27. Baldassarre ME, Di Mauro A, Mastromarino P, Fanelli M, Martinelli D, Urbano F, et al. Administration of a multi-strain probiotic product to women in the perinatal period differentially affects the breast milk cytokine profile and may have beneficial effects on neonatal gastrointestinal functional symptoms. A randomized clinical trial. Nutrients. 2016;8(11):677. [Crossref] [Pubmed] [PMC]
28. Iacovou M, Mulcahy EC, Truby H, Barrett JS, Gibson PR, Muir JG. Reducing the maternal dietary intake of indigestible and slowly absorbed short-chain carbohydrates is associated with improved infantile colic: a proof-of-concept study. J Hum Nutr Diet. 2018;31(2):256-65. [Crossref] [Pubmed]
29. Iacovou M, Craig SS, Yelland GW, Barrett JS, Gibson PR, Muir JG. Randomised clinical trial: reducing the intake of dietary FODMAPs of breastfeeding mothers is associated with a greater improvement of the symptoms of infantile colic than for a typical diet. Aliment Pharmacol Ther. 2018;48(10):1061-73. [Crossref] [Pubmed]
30. Srinivasjois R, Rao S, Patole S. Prebiotic supplementation in preterm neonates: updated systematic review and meta-analysis of randomised controlled trials. Clin Nutr. 2013;32(6):958-65. [Crossref] [Pubmed]
31. Aslan NN, Yardımcı H. Anne sütü ve mikrobiyota [Breast milk and microbiota]. Turkiye Klinikleri J Nutr Diet-Special Topics. 2017;3(2):95-100. [Link]
32. Rhoads JM. Probiotic Lactobacillus reuteri effective in treating infantile colic and is associated with inflammatory marker reduction. J Pediatr. 2018;196:324-7. [Crossref] [Pubmed]
33. Anabrees J, Indrio F, Paes B, AlFaleh K. Probiotics for infantile colic: a systematic review. BMC Pediatr. 2013;13:186. [Crossref] [Pubmed] [PMC]
34. Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. Arch Med Sci. 2018;14(5):1137-43. [Crossref] [Pubmed] [PMC]