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The Effect of Probiotic in Treatment of Infantile Colic: A Randomized Clinical Trial

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Abstract

Background: Infantile colic imposes a heavy financial burden on families and the healthcare system. This study was conducted to evaluate the effect of Pedilact on the treatment of infantile colic.

Materials and Methods: In this randomized clinical trial, 84 infant younger than 3 months with infantile colic were divided in two groups of 42 cases each- probiotic and standard treatment. This study was done in Arak city, Iran between 2013 and 2016. The population of the study consisted of breastfed infants and formula-fed infants younger than 3 months (less than 13 weeks) who referred to Amir Kabir Hospital and pediatric clinics presenting crying and restlessness symptoms consistent with the modified Wessel criteria. In the treatment group, in addition to the main treatment, five drops of Pedilact (Iran) was daily administered for 28 days. In both groups, the main treatment was instructed to the parents and they were advised to do the following techniques to pacify the infant: making relaxing sounds or vocals, applying peaceful and rhythmic rocking motion, walking, and using mild tremor-like movements.

Results: In Pedilact and control groups, 54.75% and 28.57% of the cases were male, respectively. 23 infants (75.61%) in the Pedilact group and 33 infants (82.5%) in the control group were breastfed infants. The mean age of infants in Pedilact and control groups were 6.64 $\pm$ 2.90 and 6.69 $\pm$ 5.97, respectively. There was no significant difference between the Pedilact and control groups in terms of mean duration of crying time during a day (P= 0.075), and the number of crying attacks per day (P= 0.127), there was a significant decrease in both variables over time, but the mean for hours of sleep in the group receiving the standard treatment was significantly higher than that of the group receiving Pedilact (P= 0.001).

Conclusion: There was no significant difference between the control and Pedilact groups in terms of crying time during a day and the number of crying attacks. It should be mentioned that, in this study, sample size was relatively low; hence, a multicenter study is recommended.

***Key Words*:** Colic, Infant, Pedilact, Probiotics.

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1- INTRODUCTION

Infantile colic is prevalent and stressful for families (1). According to Wessel criteria, it is characterized by crying and restlessness ≥ 3 hours a day for ≥ 3 days per week for ≥ 3 weeks (2) which involves more than 20% of infants less than 3 months old (3-6). Infantile colic imposes a heavy financial burden on families and the healthcare system. Trouble sleeping and crying in the first three months of their lives is the most frequent cause of families' referring to healthcare centers (7). Infantile colic also has significant effects on the mental health of the mother and the quality of life of the family (8, 9).

It is also considered as a factor in child abuse (10, 11). Infants whose crying and restlessness last more than 3 months are at risk of anxiety, aggression, hyperactivity, allergies, and sleep disorders at school (12, 13). Finding an effective strategy for treating infantile colic can dramatically reduce its associated morbidity and improve the quality of family life. After 50 years of research on infantile colic, its etiology still remains unknown (1). Likewise, it is still unclear whether infantile colic is an extreme form of normal crying, a sign of underlying physiological problem, or a psychosocial factor (14). A potential mechanism can be the infant's gut microbiota change with allergies to cow's milk protein (15, 16).

Recent research has focused on the effects of gut microbiota pathophysiology on intensifying the baby's crying (1). One study found that the rate of *Clostridium difficile* in the stool of the infants with colic is more than that of the control group (17), whereas two other studies reported increased *Escherichia coli* and decreased *Lactobacillus* strains in infants with colic as compared to the control group (18, 19). Despite the fact that *Bifidobacterium* and *Lactobacillus* strains have been shown to have a protective role against crying (20), in another study, *Lactobacillus* strains were increased in infants with colic compared to the control group (21). Differences in gut microbiota can lead to such mechanical changes as gas, belching, and intestinal motility disorders (22, 23) which, in turn, contribute to infants' crying. The etiology of infantile colic is, therefore, considered to be multi-factorial (1). Using probiotics is one of the treatments for infantile colic (1). Probiotics are live microorganisms (24) which are colonized in the intestines, compete with other bacteria in connection, stimulate the host immune response to pathogens, reduce intestinal inflammation, increase mucosal surfaces, reinforce the mucosal barriers, and regulate the infants' gut microbiota (1). Despite the fact that probiotics present some positive evidence of the management of functional gastrointestinal disorders, such evidence is not compelling enough to recommend their prescription (25). A recent study revealed that certain strains of Lactobacillus can inhibit the growth of gas-producing coliform in infants with colic; probiotic and probiotics can also bring about changes in the gastric intestinal motility in infants by stimulation of gastric emptying (22, 23).

Animal studies have demonstrated that probiotics can alter the perception of pain in the intestines and inhibit the contractile activity of intestines in mice (1). According to some studies certain childhood diseases are associated with microbiome alterations, namely necrotizing enterocolitis, infantile colic, asthma, atopic disease, gastrointestinal disease, diabetes, malnutrition, mood/anxiety disorders, and autism spectrum disorders. Treatment studies suggest that probiotics are potentially protective against the development of some of these diseases. Timing and duration of treatment, the optimal probiotic strain (s), and factors that may alter the composition and function of the

microbiome are still in need of further research (26). Probiotic interventions in early life can be recommended for prevention in healthy offspring and those at risk of chronic disease (27). Although the effect of probiotics on the treatment of infantile colic is not conclusive (24), the aim of this study was to evaluate the effect of probiotics (Pedilact) on the treatment of infantile colic.

2- MATERIALS AND METHODS

2-1. Trial design

The present study was a single-blind randomized clinical trial study designed in parallel (IRCT number: 2016111023876N3). The method of analysis in this study was the intention to treat.

2-2. Participants

The population of the study was composed of younger than 3 months (less-than-13-week) breastfed infants and formula-fed infants who referred to Amir Kabir Hospital and Pediatricians Clinic showing crying and restlessness symptoms consistent with the modified Wessel criteria. Having met the inclusion criteria for entering the study with their parents' consent, they were included in the study between 2013 and 2015 (24 months). Diagnosis and treatment of colic in infants was done by pediatrics specialists.

Inclusion criteria for the study were having the infantile colic (based on Wessel criteria including crying and restlessness ≥ 3 hours a day for ≥ 3 days per week for ≥ 3 weeks), being younger than three months (less than 13 weeks) at the time of the study, gestational age of more than 36 weeks at birth, and the birth weight of more than 2,500 grams. Exclusion criteria were growth retardation failure to thrive (FTT) average weight gain of less than 100 grams per week from birth to the most recent measurement taken, immune compromise, genetic disorders, significant growth, Kidilact or Pedilact consumption by formula-fed infants during the study period, Kidilact or Pedilact consumption by breastfed infants' mothers, and lack of adequate literacy to complete the questionnaires.

2-3. Interventions

In both groups, the main treatment was instructed to the parents and they were advised to do the following techniques to pacify the infant: making relaxing sounds or vocals, applying peaceful and rhythmic rocking motion, walking, using mild tremor-like movements like those of the cars, minimizing such aggressive responses as quick flicks or parents' putting the infant in cloths and rotating it fast. In the treatment group, in addition to the above-mentioned techniques, five drops of Pedilact daily (10^9cfu) was administered for 28 days (Iran, Zist Takhmir), while in the control group, just the mentioned techniques were recommended.

2-4. Outcome

The desired outcomes in both groups were measured on days 1, 7, 14, 21, and 28. In both groups, the number of infants' crying and those having restless attacks with crying times during 24 hours on days 1, 7, 14, 21 and 28 were also measured. Moreover, on days 1, 7, 14, 21, and 28, the families were contacted by a trained intern to remind them of filling out the data collection forms.

2-5. Sample size

By considering the Type I error 0.05 (Alpha=0.05), 80% power (beta=0.20), 10% probability of loss to follow up and to find a 3% difference (d=3%), the sample size for each group was estimated 42 infants. Eventually, a total of 84 eligible infants were included in the study.

2-6. Randomization and sequence generation

The participants were allocated to two groups through balanced block randomization technique. For this purpose, some blocks of six were used. The allocation of the participants into three groups was carried out with the help of Sealed Envelope online application (13). In this study, due to the fact that balanced block randomization was used and unique codes were assigned to each person, allocation concealment was obtained. As a result of random allocation, distribution of potential confounding variables between the two groups was to be identical, and their confounding role was controlled.

2-7. Ethical Consideration

Before entering the study, all patients were provided with adequate information about the study, their informed consent was obtained, and the patients were free to withdraw from the study. The research groups were required to observe all of the provisions of the Declaration of Helsinky and to comply with the statements of Arak University of Medical Sciences on research ethics. Moreover, parents' written consent was obtained for infants.

2-8. Implementation

Random allocation sequence was generated by the fellow methodologist using the Sealed Envelope Website. Inclusion and allocation of the patients was conducted by our emergency resident under the supervision of the main person in charge for the project.

2-9. Blinding

In this study, the person in charge of measuring the outcomes of different groups and the statistical analyst were both blind to the allocation of the participants to different groups.

2-10. Statistical procedure

The qualitative and quantitative data were respectively reported and described as means (standard deviations) and numbers (percent). Data analysis was carried out using Stata 13 software running such statistical tests as independent samples t-test (for comparing the continuous variables in both groups), Chi-square (for comparing the categorical variables in both groups), and generalized estimating equations (GEE) (for assessing the repeated measure variables, including the duration of crying time during one day and the number of crying attacks per day). Alpha coefficient of less than 0.05 was set as the significance level.

3- RESULTS

In this study, 84 infants entered the final analysis. There were 42 infants in Pedilact and control groups. The comparison of baseline data (**Table.1**) indicated that the randomization process had created two identical groups. Although there was no significant difference between the two groups in age, birth weight, weight at first visit and the type of feeding, the two groups were different in terms of the gender distribution (P= 0.015).

Hence, the role of gender in the analysis was controlled. The infants were studied considering their growth disorders, genetic disorders, immune compromise, history of antibiotic use, and history of taking probiotics during the last two weeks; no such cases were found in any of the groups. Such desired outcomes as infants' crying time during the day, the number of crying attacks per day, and sleeping time for the two groups were compared at the baseline. No significant difference was observed between the two groups in terms of these variables.

In **Table.2**, both groups were contrasted pertaining to infants' crying time during the day, the number of crying attacks per day, and sleeping time during the follow-up times (the baseline, days 7, 14, 21, and 28). Generalized estimating equations test revealed that while there was no

significant difference between the two groups in terms of mean duration of crying time during a day (P= 0.075) and the number of crying attacks per day (P= 0.127), there was a significant decrease in both variables over time. Concerning the mean for sleeping hours per day, there was a significant difference between the two groups in a way that the mean for hours of sleep in the group receiving the standard treatment was significantly higher than that of the group receiving Pedilact (P= 0.001); the mean for sleeping hours per day did not present any significant change in both groups over time (P= 0.620).

Table-1: Comparison of baseline data based on two groups

Variables		Pedilact Group	Control group	P- value
Gender*	Male Female	23 (54.76) 19 (45.24)	12 (28.57) 30 (71.43)	0.015
Feeding*	Mother milk Formula Mix Milk	31 (75.61) 4 (9.76) 6 (14.63)	33 (82.5) 1 (2.50) 6 (15)	0.396
Age#		6.64±2.90	6.69±5.97	0.933
Birth weight#		3.18±0.34	3.21±0.30	0.670
Weight in the 1st visit#		4.62±0.77	4.38±0.58	0.123
Cry Attack Numbers at the 1st day#		4.62 (2.11)	4.88 (1.99)	0.559
Crying Time at the 1st day (Hour) #		6.14 (4.65)	7.10 (4.06)	0.322
Sleep Time at the 1st day (Hour) #		16.57 (1.64)	15.93 (2.21)	0.134

* Number (Percent); Chi square test; # Mean (Standard Deviation); Two independent t-test.

Table-2: The means of main outcome at different times for Pedilact and control groups

Variables	Pedilact	Control	P- value
Cry Attack Numbers (Mean)			P for groups=0.127 P for time= 0.001
Baseline	4.88 (1.99)	4.62 (2.11)	
7th day	6.87 (3.69)	5.69 (4.25)	
14th day	5.03 (2.92)	4.31 (3.26)	
21st day	3.58 (3.01)	2.64 (2.55)	
28th day	2.12 (2.69)	1.34 (2.03)	
Crying Time (Hour)			P for groups=0.075 P for time= 0.001
Baseline	7.10 (4.06)	6.14 (4.65)	
7th day	5.02 (1.75)	4.41 (1.94)	
14th day	3.85 (2.12)	3.34 (1.98)	
21st day	2.87 (2.42)	2.03 (1.59)	
28th day	1.85 (2.43)	1.10 (1.47)	
Sleep Time (Hour)			P for groups=0.001 P for time= 0.620
Baseline	15.93 (2.21)	16.57 (1.64)	
7th day	15.74 (1.97)	16.72 (1.48)	
14th day	15.35 (2.01)	17.22 (1.04)	
21st day	15.20 (3.18)	17.41 (0.91)	
28th day	14.69 (2.06)	17.45 (1.10)	

4- DISCUSSION

This study examined the effect of probiotics in the treatment of infantile colic in the infants with colic the results of which indicated that while there was no significant difference between the standard treatment and taking Pedilact in terms of crying time during a day and the number of crying attacks at different times, there was a significant reduction in both variables over time. In addition, a significant difference was found between sleeping hours in the two groups in a way

that the mean for hours of sleep in the group receiving the standard treatment was significantly higher that of the group receiving Pedilact. The mean for sleeping hours per day did not show any significant change in both groups over time. As shown in the results, there was a significant difference between the mean duration of crying time during a day and the number of crying attacks per day, which reflects the positive effect of both treatments in treating the infantile colic. However, no significant difference was found between the two treatments. Given that the mean for sleeping hours in the group receiving the standard treatment was significantly higher that of the group receiving Pedilact, taking Pedilact has no precedence over the standard treatment.

Probiotics in the near future may have a critical role in some functional gastrointestinal disorders in infants and children. The main limitations for the recommendation by institutions are the methodological issues that limit the quality of the evidence and the heterogeneity of treatments (probiotic strain and dose, dose and duration of supplementation, primary outcomes, etc). Some specific strains are promising for infant colic (L. reuteri DSM 17938) and irritable bowel syndrome (28).

Savino et al. (2010) examined 50 infants based on the Wessel criteria, giving a group L reuteri DSM 17938 probiotic and the other group a placebo for 21 days (29). The results demonstrated that the used probiotics could improve the symptoms of infantile colic as compared to the placebo, whereas in our study, Pedilact was not effective to improving symptoms of colic compared to control group. Dupont et al. (30) also conducted a study in 2010 studying 66 healthy infants diagnosed with colic, randomly divided into two groups of probiotics and placebo for a month. In their study, infants tolerated the probiotics well, showing an appropriate weight and height increase. In our study, also, the infants tolerated the probiotics well, and their average hours of crying and the average number of crying attacks per day decreased, but Pedilact was not effective to improving symptoms of colic. Sung (2015) in a review study showed that although L reuteri DSM 17938 probiotic can be effective for certain groups of breastfed infants with colic, it is not recommended for formula-fed infants (31). In our study, however, despite the fact that the number of formula-fed infants in the treatment group was small, they tolerated the probiotic drug well.

Moreno et al. (32) also found that L reuteri DSM 17938 probiotic had a significant impact on the improvement of infantile colic. Likewise, studying 50 infants with infantile colic, Nourbakhsh et al. (33) found that the success of medical treatment was 87 percent for a synbiotic drug and 46 percent for the placebo group at the end of a one-month treatment. In a recent meta-analysis on the probiotic Lactobacillus reuteri, breastfed infants with colic receiving a daily dose of 108 colony forming units cried an average of 56 minutes/day less than those in the control group at day 21 following the initiation of the treatment (34). This finding is not similar to our study results probably due to the presence of breast-fed and formula-fed participants in our study.

In a review article by Scherek et al. which consisted of five randomized clinical trial studies 2 different strains of the probiotic Lactobacillus reuteri were assessed in frequently breastfed infants. The analysis of response rates indicated that infants receiving probiotics had a 2.3 times greater chance of experiencing a 50% or greater decrease in crying/fussing time compared to controls (35). Data summarized in a review by Szajewska revealed that L reuteri DSM 17938 could be effective in the reduction of crying/colic both in breastfed and formula-fed infants (36). Since the results of the present study

showed no significant difference between the use of Pedilact and the common treatment for the infantile colic, it is recommended some further clinical trials using non-inferiority or equivalence methods be conducted to assert that these two methods have the same effect.

4-1. Limitations of the study

Of the limitations of this study which can be noted is that it is probable that in some cases in both groups, due to excessive crying in the infants, the parents may have used such other interventions as other drugs. It is also recommended that some further studies be carried out with larger sample sizes in order to achieve more accurate results.

5- CONCLUSION

As shown in the results section of the study, a significant trend was found between the mean duration of crying time during a day and the number of crying attacks per day over a study period, which reflects the positive effect of both treatments in treating the infantile colic. There was, however, no significant difference between the two treatments. Provided that the mean for sleeping hours in the group receiving the standard treatment was significantly higher that of the group receiving Pedilact, taking Pedilact has no precedence over the standard treatment.

6- AUTHORS CONTRIBUTIONS

FD, SMH, MT and AAH conceptualized the study design and FD and SMH coordinated and supervised the study. AAH, SS and MT oversaw the sample collection and analyzing and interpreting the data. AAH, SS and MT drafted the article. SMH and FD critically revised the manuscript for important intellectual content and provided final approval of the version to be published. All authors approved the final draft before publication.

7- CONFLICT OF INTEREST

All the authors of the study have no conflict of interest.

8- ACKNOWLEDGMENTS

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9- REFERENCES

1. 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 pediatrics 2012;12(1):1.

2. Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiler AC. Paroxysmal fussing in infancy, sometimes called" colic". Pediatrics 1954;14(5):421-35.

3. Lucassen P, Assendelft W, van Eijk JTM, Gubbels J, Douwes A, Van Geldrop W. Systematic review of the occurrence of infantile colic in the community. Archives of disease in childhood 2001;84(5):398-403.

4. Wake M, Morton-Allen E, Poulakis Z, Hiscock H, Gallagher S, Oberklaid F. Prevalence, stability, and outcomes of cry-fuss and sleep problems in the first 2 years of life: prospective community-based study. Pediatrics 2006;117(3):836-42.

5. Bahrami H, Kiani MA, Noras M. Massage for Infantile Colic: Review and Literature. International Journal of Pediatrics 2016;4(6):1953-8.

6. Mohammadian Dameski M, Mehri M, Feyzabadi Z. Flatulent Foodstuff, an Agent in the Creation of Infantile Colic: a Narrative Study based on the Traditional Iranian Medicine and Modern Investigation. International Journal of Pediatrics 2017;5(2):4285-93.

7. Morris S, St James-Roberts I, Sleep J, Gillham P. Economic evaluation of strategies

for managing crying and sleeping problems. Archives of disease in childhood 2001;84(1):15-9.

8. McMahon C, Barnett B, Kowalenko N, Tennant C, Don N. Postnatal depression, anxiety and unsettled infant behaviour. Australian and New Zealand Journal of Psychiatry 2001;35(5):581-8.

9. Smart J, Hiscock H. Early infant crying and sleeping problems: A pilot study of impact on parental well-being and parent-endorsed strategies for management. Journal of paediatrics and child health 2007;43(4):284-90.

10. Barr RG, Trent RB, Cross J. Age-related incidence curve of hospitalized shaken baby syndrome cases: convergent evidence for crying as a trigger to shaking. Child abuse and neglect 2006;30(1):7-16.

11. Lee C, Barr RG, Catherine N, Wicks A. Age-related incidence of publicly reported shaken baby syndrome cases: is crying a trigger for shaking? Journal of Developmental and Behavioral Pediatrics 2007;28(4):288-93.

12. Savino F, Castagno E, Bretto R, Brondello C, Palumeri E, Oggero R. A prospective 10-year study on children who had severe infantile colic. Acta Paediatrica 2005;94(s449):129-32.

13. Wolke D, Rizzo P, Woods S. Persistent infant crying and hyperactivity problems in middle childhood. Pediatrics 2002;109(6):1054-60.

14. Hiscock H, Jordan B. 1. Problem crying in infancy. Medical journal of Australia 2004;181(9):507.

15. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy–a Spanish prospective case–control 6-month follow-up study. Pediatric Allergy and Immunology 2010;21(2p2):e394-e400.

16. Thompson-Chagoyan OC, Fallani M, Maldonado J, Vieites JM, Khanna S, Edwards C, et al. Faecal Microbiota and Short-Chain Fatty Acid Levels in Faeces from Infants with Cow's Milk Protein Allergy. International archives of allergy and immunology 2011;156(3):325-32.

17. Lehtonen L, Korvenranta H, Eerola E. Intestinal microflora in colicky and noncolicky infants: bacterial cultures and gas-liquid chromatography. Journal of pediatric gastroenterology and nutrition 1994;19(3):310-4.

18. Savino F, Cordisco L, Tarasco V, Calabrese R, Palumeri E, Matteuzzi D. Molecular identification of coliform bacteria from colicky breastfed infants. Acta Paediatrica 2009;98(10):1582-8.

19. Savino F, Cresi F, Pautasso S, Palumeri E, Tullio V, Roana J, et al. Intestinal microflora in breastfed colicky and non-colicky infants. Acta paediatrica 2004;93(6):825-9.

20. Pärtty A, Kalliomäki M, Endo A, Salminen S, Isolauri E. Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. PloS one 2012;7(3):e32495.

21. Savino F, Bailo E, Oggero R, Tullio V, Roana J, Carlone N, et al. Bacterial counts of intestinal Lactobacillus species in infants with colic. Pediatric allergy and immunology 2005;16(1):72-5.

22. 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 microbiology 2011;11(1):1.

23. Indrio F, Riezzo G, Raimondi F, Bisceglia M, Cavallo L, Francavilla R. Effects of probiotic and prebiotic on gastrointestinal motility in newborns. J Physiol Pharmacol 2009;60(Suppl 6):27-31.

24. Wallace B. Clinical use of probiotics in the pediatric population. Nutrition in Clinical Practice 2009;24(1):50-9.

25. Vandenplas Y, Alturaiki MA, Al-Qabandi W, AlRefaee F, Bassil Z, Eid B, et al. Middle East Consensus Statement on the Diagnosis and Management of Functional Gastrointestinal Disorders in <12 Months Old

Infants. Pediatric Gastroenterology, Hepatology and Nutrition 2016;19(3):153-61.

26. Slattery J, MacFabe DF, Frye RE. The Significance of the Enteric Microbiome on the Development of Childhood Disease: A Review of Prebiotic and Probiotic Therapies in Disorders of Childhood. Clinical medicine insights Pediatrics 2016;10:91-107.

27. Hashemi A, Villa CR, Comelli EM. Probiotics in early life: a preventative and treatment approach. Food and function 2016;7(4):1752-68.

28. Francavilla R, Cristofori F, Indrio F. Indications and Recommendations by Societies and Institutions for the Use of Probiotics and Prebiotics in Paediatric Functional Intestinal Disorders. Journal of pediatric gastroenterology and nutrition 2016;63 Suppl 1:S36-7.

29. Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics 2010;126(3):e526-e33.

30. Dupont C, Rivero M, Grillon C, Belaroussi N, Kalindjian A, Marin V. α-Lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance. European journal of clinical nutrition 2010;64(7):765-7.

31. Sung V. Probiotic interventions in infantile colic. Current Opinion in Clinical Nutrition and Metabolic Care 2015;18(3):307-11.

32. Pérez-Moreno J, Taboada CL, Tolín HM, Sánchez SC, Álvarez-Calatayud G. Probiotics for the treatment of infant colic: a clinical case. Nutricion hospitalaria 2014;31:78-82.

33. Kianifar H, Ahanchian H, Grover Z, Jafari S, Noorbakhsh Z, Khakshour A, et al. Synbiotic in the management of infantile colic: a randomised controlled trial. Journal of paediatrics and child health 2014;50(10):801-5.

34. Dassow P, Fox S. When can infants and children benefit from probiotics? The Journal of family practice 2016;65(11):789-94.

35. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the Treatment of Infantile Colic: A Systematic Review. J Pharm Pract. 2017; 30(3):366-374.

36. Szajewska H, Dryl R. Probiotics for the Management of Infantile Colic. Journal of pediatric gastroenterology and nutrition 2016;63(1S):S22-S4.