

Examination with immune checkpoint molecules PD-L1 in the pancreatic ductal adenocarcinoma

Minezaki, S.^{1*}, Ilnuma, H.¹, Tamura, S.¹, Miura, F.¹, Sano, K.¹

Infectious Diseases Research Center, Kashan University of Medical Sciences, Kashan, Iran¹

Corresponding author: 1*



Keywords:

Infantile colic; nutrition;
formula; breast milk

ABSTRACT

Infantile colic is one of the most common causes of mothers' referral to physicians and pediatricians for treatment of their infants. This disorder is characterized as unnatural excessive crying which has been mostly observed during the first three months of birth among 8-40% of infants. Cow milk and cow milk formula are the main causes of infantile colic. This study attempts to evaluate the relationship of type of nutrition with the occurrence of infantile colic. This case-control study was carried out on infants referred to the pediatric clinics throughout Kashan during 2013. One hundred infants with colic were classified as cases and one hundred healthy individuals matched with patients in age and gender, were considered as controls. Parents of the two groups were asked about type of nutrition of their infants. According to the type of nutrition, the infants were included in one of three groups merely breast-fed, breast-fed and formula-fed and merely formula-fed infants. Correlation of type of nutrition with infantile colic was then determined in the study. Chi-square was used to analyze the data. No significant differences were observed between the two groups in terms of age and gender. 69 (69%), 8 (8%), and 23 (23%) of the infants in the case group were breast-fed, breast-fed and formula-fed, and formula-fed, respectively. Whereas in the control group 90 (90%), 8 (8%), and 2 (2%) of the infants were breast-fed, breast-fed and formula-fed, and formula-fed, respectively ($P < 0.0001$). Our study confirmed that the occurrence of infantile colic is associated with formula feeding. In other words, formula-fed infants were at more risk of infantile colic than the others.



This work is licensed under a Creative Commons Attribution Non-Commercial 4.0 International License.

1. INTRODUCTION

The word "colic" is derived from the ancient Greek word for intestine (sharing the same root as the word "colon"). Infantile colic is one of the most common causes of visits by physicians and pediatricians. This disorder is characterized as excessive crying which has been mostly observed during the first three months of birth among 5- 40% of infants [1- 5]. According to Wessel, Colic is often defined by the "rule of three": crying for more than three hours per day, for more than three days per week, and for longer than three weeks in an infant who is well-fed and otherwise healthy. The physician's role is to ensure that there is no organic cause for the crying, offer balanced advice on treatments, and provide support to the family. Colic

is a diagnosis of exclusion that is made after performing a careful history and physical examination to rule out less common organic causes [6- 9]. With colic, periods of crying most commonly happen in the evening and for no obvious reason. Associated symptoms may include legs pulled up to the stomach, a flushed face, clenched hands, and a wrinkled brow. The cry is often high pitched (piercing). Persistent infant crying has been associated with severe marital discord, postpartum depression, early termination of breastfeeding, frequent visits to doctors, maternal smoking and over a quadrupling of excessive laboratory tests and prescription of medication for acid reflux. The cause of colic is generally unknown. Fewer than 5% of infants who cry excessively turn out to have an underlying organic disease, such as constipation, gastroesophageal reflux disease, lactose intolerance, cows' milk allergy, anal fissures, subdural hematomas, or infantile migraine [10- 14]. Various causes are associated with occurrence of this disorder of which psychological, digestive, and hormonal factors have been paid more attention. However, different studies have revealed different results in this respect [15- 19]. Type of nutrition is highly responsible for this disorder, while breast milk has been mentioned as a preventive factor in this regard (24- 26). But some researchers indicate that it occurs equally in breast- and bottle-fed infants [20- 23]. Nevertheless, due to the contradicting results, further studies are required. Therefore, we have focused on the relationship of type of nutrition with the occurrence of infantile colic in order to offer a preventive therapeutic way to both physicians and parents.

2. MATERIALS AND METHODS

This analytical case-control study was carried out on outpatient cases referred to the pediatric clinics throughout Kashan during 2013. Sample size was estimated based on a previous study in which the rate of non-exclusive breastfed was 11 in colicky group and 37 in non-colicky group [7]. Then 180 samples were estimated to be needed based on the following parameters ($\alpha = 0.05$, $\beta = 0.80$ and sampling error of 0.05). However, 200 subjects were participated in the study. One hundred infants with colic were classified as cases and one hundred healthy individuals matched with patients in age and gender, were considered as controls. The study population was those colicky infants selected according to Wessel's definition. Inclusion criteria were aged 1-3 months, lack of constipation, lack of gastroesophageal reflux disease, lack of lactose intolerance, lack of cows' milk allergy, lack of anal fissures or other pathologic findings. Infants who their parents did not consent to fill out the questionnaire were excluded from the study. For each colicky infant one normal infant without colic was included in the control group. Age-matched and sex-matched control was recruited per case, using specific criteria. All cases of study have been used Cow milk protein-based formulas. Parents of the infants in each group were asked about their type of nutrition. According to the type of nutrition, the infants were included in one of three groups: merely breast-fed, breast-fed and formula-fed and merely formula-fed infants. Correlation of type of nutrition to the infantile colic was determined using Statistical methods.

2.1 Statistical analysis

The statistical analysis was performed using SPSS software version 13 (SPSS Inc., Chicago Illinois, USA). Chi- square and t-test was used for comparison the gender and age between two groups. For reporting of results only variables with a P value less than or equal to 0.05 was considered significant.

3. RESULTS

200 infants including 100 infants in the case group (colicky infants) and 100 infants in the control group were studied. Mean ages of the infants were 24.8 and 26.1 days in the case and control groups, respectively denoting no significant statistical difference ($p > 0.05$). The case group included 47 and 53 male and female infants, respectively. Also, the control group included 49 and 51 male and female infants, respectively which showed no meaningful difference ($p > 0.05$). In the case group, 69, 8, and 23 percent of the infants

were breast-fed, breast-fed and formula-fed, and merely formula-fed, respectively. Whereas in the control group 90%, 8%, and 2% of the infants were breast-fed, breast-fed and formula-fed, and formula-fed, respectively. Comparison of these findings reveal a significant difference ($P < 0.0001$) (Table 1).

Table 1. Prevalence and rate of type of nutrition in both groups

Study Group type of nutrition	Case	Control	P value
	N (%)	N (%)	
Breast milk only	69 (%69)	90 (%90)	P<0.0001*
Breast milk & Formula	8 (%8)	8 (%8)	
Formula only	23(%23)	2(%2)	

* Chi-square test

4. DISCUSSION

Our study confirmed that the occurrence of infantile colic is associated with formula feeding. In other words, formula-fed infants were at more risk of infantile colic than the others. Formulas available on the market are mainly produced from cow milk and are changed based on the infants' needs and tolerance for cow milk protein. Different studies have shown that since cow milk is the main nutrition except for breast milk, sensitivity to cow milk is the main allergy common among infants with specific clinical signs [22- 24] which are probably associated with the occurrence of infantile colic. Some studies have revealed that formula-fed infants may be at risk of infantile colic due to their allergy to cow milk protein [19], [20]. This association has been confirmed in our study as well. In a study conducted by A on 196 formula-fed and 204 breast-fed colicky infants in 2011 in Kerman, Iran it was revealed that breast milk compared to formula-fed infants was is less proneto colic (47.1% vs. 62.2%) [25]. In Iran in 2008 showed that colicky and non-colicky infants had no significant difference according to infant's feeding pattern [7]. In London in 2010 showed that colic occurs equally inbreast- and bottle-fed infants, and in both sexes [22]. In Italy in 2006 reported that the use of a partially hydrolysed formula induces a reduction of crying episodes in infants with colic after 7 and 14 days when compared with a standard formula [26]. Our study showed that there was a relationship between the formula feeding and the occurrence of colic. In other words, formula-fed infants are more at risk of infantile colic. As stated before, most researchers believe in factors acting sometimes sinergically. A number of health organizations recommend breastfeeding as the best choice for babies. Breastfeeding helps defend against infections, prevent allergies, and protect against a number of chronic conditions including colic. Beyond that, breastfeeding is encouraged until at least 12 months. Formal breastfeeding education is recommended which is provided the breastfeeding information given as part of standard antenatal care, and which may include individual or group education sessions led by peer counselors or health professional and nurses. There is some limitation in this study. One of them is that mother's diet have not controlled in our study. So, it is recommended that some factors (i.e. mother's diet) should be considered in future studies. Also conduction of further studies considering other variables that contribute to this complication can make clear some of the ambiguities concerning etiology of the infantile colic.

5. CONCLUSION

According to our findings, there is a causal relationship between infantile colic and formula feeding. According to research, breastfeeding carries many health benefits for infants and mothers. This study suggest that breastfeeding may reduce the risk of colic in infantile.

6. REFERENCES

- [1] Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran's Gastrointestinal and Liver Disease-2 Volume Set: Pathophysiology, Diagnosis, Management, 10th Edition. Philadelphia WB: Saunders; 2016.

- [2] Marcdante KJ, Kliegman RM. Nelson Essentials of Pediatrics. 7th Edition, Philadelphia: Elsevier Saunders; 2015.
- [3] Dobson D, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. *Cochrane Database Syst Rev*. 2012;12:CD004796.
- [4] Landgren K, Raith W, Schmölder GM, Skjeie H, Skonnord T. Acupuncture in the treatment of infantile colic. *Ital J Pediatr*. 2015;41: Page1.
- [5] Indrio F, Di Mauro A, Riezzo G, Cavallo L, Francavilla R. Infantile colic, regurgitation, and constipation: an early traumatic insult in the development of functional gastrointestinal disorders in children? *Eur J Pediatr*. 2015;174(6):841-2.
- [6] Zwart P, Vellema-Goud MG, Brand PL. Characteristics of infants admitted to hospital for persistent colic, and comparison with healthy infants. *Acta. Paediatr*, 2007;96(3):401-5.
- [7] Talachian E, Bidari A, Rezaie MH. Incidence and risk factors for infantile colic in Iranian infants. *World J Gastroenterol*. 2008;14(29):4662-6.
- [8] Kheir AE. Infantile colic, facts and fiction. *Ital J Pediatr*. 2012; 38:34.
- [9] Roberts DM, Ostapchuk M, O'Brien JG. Infantile colic. *Am Fam Physician*. 2004;70(4):735-40.
- [10] Batchelor N, Kelly J, Choi H, Geary B. BET 2: Probiotics and crying time in babies with infantile colic. *Emerg Med J*. 2015;32(7):575-6.
- [11] Mi GL, Zhao L, Qiao DD, Kang WQ, Tang MQ, Xu JK. Effectiveness of *Lactobacillus reuteri* in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. *Antonie Van Leeuwenhoek*. 2015;107(6):1547-53.
- [12] Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics* 2008;121(5):1062-8.
- [13] Heine RG. Gastroesophageal reflux disease, colic and constipation in infants with food allergy. *Curr Opin Allergy Clin Immunol* 2006;6(3):220-5.
- [14] Çak HT, Karabekiroğlu K, ÇengelKültür E, Tarakçıoğlu MC, Kaya R, Say GN, et al. Relationship between the Psychiatric Symptoms in Expecting Parents and Postpartum Depression and Infantile Colic: A Multicenter Follow up Study. *Turk PsikiyatriDerg*. 2015;26(2):87-98.
- [15] Kaymaz N, Uzun ME, Cevizci S, Yıldırım Ş, İlçin M, Topaloğlu N, et al. Uneasy child: is there any relationship between infantile colic during infancy and adhd later? *Minerva Pediatr*. 2015.
- [16] Nocerino R, Pezzella V, Cosenza L, Amoroso A, Di Scala C, Amato F, et al. The controversial role of food allergy in infantile colic: evidence and clinical management. *Nutrients*. 2015;7(3):2015-25.
- [17] Sillanpää M, Saarinen M. Infantile colic associated with childhood migraine: A prospective cohort

study. Cephalalgia. 2015.

- [18] Gelfand AA. Infant colic-a baby's migraine? Cephalalgia. 2015; pii: 0333102415576224. [Epub ahead of print]. [PMID:25733672].
- [19] Akman I, Kusçu K, Ozdemir N, Yurdakul Z, Solakoglu M, Orhan L, et al. Mothers' postpartum psychological adjustment and infantile colic. Arch Dis Child 2006;91(5):417-9.
- [20] Savino F, Ceratto S, Poggi E, Cartosio ME, Cordero di Montezemolo L, Giannattasio A. Preventive effects of oral probiotic on infantile colic: a prospective, randomised, blinded, controlled trial using Lactobacillus reuteri DSM 17938. Benef Microbes. 2015;6(3):245-51.
- [21] Vandenplas Y, Alarcon P, Alliet P, De Greef E, De Ronne N, Hoffman I, et al. Algorithms for managing infant constipation, colic, regurgitation and cow's milk allergy in formula-fed infants. Acta Paediatr. 2015;104(5):449-57.
- [22] Shergill-Bonner R. Infantile colic: practicalities of management, including dietary aspects. J Fam Health Care. 2010;20(6):206-9.
- [23] Ewing WM, Allen PJ. The diagnosis and management of cow milk protein intolerance in primary care setting. Pediatr Nurs. 2005;31(6):486-93.
- [24] Nielsen RG, Bindslev-Jensen C, Kruse-Andersen S. Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. J Pediatr Gastroenterol Nutr. 2004;39(4):383-91.
- [25] Nouhi E, Soltaninejad A. Feeding patterns and colicky infants. Journal of qualitative Research in Health Sciences. 2011; 11 (1 and 2):51-58.
- [26] Savino F, Palumeri E, Castagno E, Cresi F, Dalmaso P, Cavallo F, et al. Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula. Eur J Clin Nutr. 2006;60(11):1304-10.