

Review Article†

Effect of Human Milk on Prevention of Necrotizing Enterocolitis

Pooya Jafari doudaran¹, Mohammad Hossein Taklif², Saeed Karimi Matlob³

1. Student Research Committee, Qom university of Medical Sciences, Qom, Iran.
2. Student Research Committee, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
3. Students Research Committee, Qom university of Medical Sciences, Qom, Iran.

***Corresponding Author:** Saeed Karimi Matlob, Students Research Committee, Qom university of Medical Sciences, Qom, Iran. <https://orcid.org/0000-0002-0258-3137>. E-mail: saiid.karimi75@yahoo.com.

Abstract:

Background: Necrotizing enterocolitis is one of the most common gastrointestinal emergencies in the neonatal period. Breastfeeding can prevent the dangerous problems caused by premature infant. Human milk is an essential element for the growth of the newborn because it is a rich source of minerals, vitamins and nutrients and factors necessary for the growth of tissues and organs of the newborn.

Methods: In this review study, using keywords such as enterocolitis, necrosis, neonatal, breastfeeding, gastrointestinal search in reputable scientific databases in Google Scholar, PubMed, ScienceDirect, Web of Science, Ovid Medline, WHO website, articles, the dissertations were published during the years 2000 to 2022 and finally 20 sources were selected and reviewed, interpreted and analyzed.

Results: Breastfeeding seems to be very important for the health of infants, because it is a method of nutrition that naturally promotes the health of infants and their mothers in various ways. NEC is one of the most important diseases of premature infants that will be improved by proper nutrition of infants and will prevent and control its occurrence and severity.

Conclusion: breastfeeding can prevent many diseases, the most important of which is necrotic enterocolitis in childhood.

Keywords: Enterocolitis, Necrosis, Neonates, Breast Milk, Gastrointestinal Tract

Submitted: 9 April 2022, Revised: 3 May 2022, Accepted: 11 June 2022

Introduction

Human milk is an essential element for the growth of a newborn infant, because it is not only a rich source of minerals, vitamins and nutrients and factors necessary for the growth of tissues and organs of the baby, but also contains an amazing combination of substances, cells which are already ready to make the baby incredibly resistant to many environmental damages.

Breastfeeding reduces the incidence of infectious diseases such as infectious diarrhea and pneumonia and non-infectious diseases such as diabetes (1). And up to 1 month in infants who are not breastfed), has a high permeability. Bacteria, cells and other immune compounds in breast milk, after passing through the baby's intestines cause the growth and maturation of gastrointestinal

lymph tissues by establishing and inducing differentiation. These compounds also prevent ectopic immunity to environmental factors, food antigens and beneficial microbes by inducing an immune tolerance mechanism (2). As a result; breastfeeding can protect your baby against food allergies, asthma and skin allergies for the rest of his life. Also, breastfeeding can prevent complications such as diarrhea that occurs in many infants after vaccination (3). Today, the immunogenic role of breast milk in premature infants has received more attention. Because breastfeeding can prevent serious problems such as bronchopulmonary dysplasia and premature retinopathy, respectively; One of the most common and important causes of death is persistent respiratory failure and blindness in premature infants. Studies such as Shoji et al. Support the hypothesis that breast milk has antioxidant properties with a protective effect against oxidative stress (4). Necrotizing enterocolitis (NEC) is one of the most common gastrointestinal emergencies in the neonatal period (5). This disease has been known as one of the most important diseases of the neonatal period since 1960 (6). NEC is more common in premature infants from the first day of birth to 3 months. Its prevalence is between the third and tenth day of birth, which occurs earlier in full-term infants (over 37 weeks of gestation). The disease has no special relationship with sex and race (7). Premature infancy is the most important risk factor for NEC in preterm infants. Necrotizing enterocolitis is one of the most important diseases of premature infants that can be prevented and controlled by proper nutrition of infants. There are two main routes for maternal-to-infant cell transmission-placental transmission and oral

transmission through lactation (8). Breast milk leukocytes, including macrophages and neutrophils survive through the infant's gastrointestinal tract and are transported to the blood, lymph nodes, spleen, and liver (9&10). Understanding the physiological importance of human milk cell transfer to infants can provide insight into the protective properties of breast milk in the prevention of diseases such as neonatal NEC. In NICU hospitals and the increase in mortality due to premature neonatal diseases, especially necrotizing enterocolitis, the aim of this review study was to evaluate the effect of human milk on the prevention of necrotizing enterocolitis. Due to current issues in the world and increasing attention to neonatal diseases as well as diseases due to premature birth and hospitalization in NICU hospitals and increasing mortality due to premature neonatal diseases, especially necrotizing enterocolitis, the purpose of this review study was to evaluate the effect of human milk in the prevention of necrotizing enterocolitis.

Materials and Methods

In this study, which was conducted by a narrative review method, using keywords including enterocolitis, necrosis, neonatal, breast milk, gastrointestinal tract by searching international scientific databases including: Pub Med, Web of Science, Google Scholar, Scopus, Elsevier, and internal scientific databases including: Barakatkn knowledge system, University Jihad scientific database, Iranian medical library (medlib), Iranian journals database (magiran), Knowledge reference (civilica) and search was done on the WHO site. A total of 58 scientific sources were collected, including books, articles, dissertations and reports that were published in Persian and English

between 2000 and 2022 on enterocolitis, necrosis, neonates, breast milk, and gastrointestinal tract. . Unrelated sources and articles were removed and sources related to our review were studied. Finally, 20 articles and scientific sources were selected and analyzed according to the purpose of the study and according to the needs of 30 articles.

Results

Human milk is better tolerated and digested by premature infants due to its effects on the gastrointestinal tract. In particular, at the time of breastfeeding, there is less stomach residue and less cessation of breastfeeding compared to formula feeding (11). Human breast milk contains a wide variety of biologically active components that are essential for infant growth, immune homeostasis, and intestinal maturity. The composition of human milk varies according to the stage of breastfeeding, the gestational age of the baby, the health of the mother and the health of the infant, and the nutritional status of the mother. Numerous studies have shown that maternal diet intake affects the concentration of vitamins and nutrients in human milk (12). These nutrients, including immunoglobulins, growth factors, cytokines, and immune cells, can be passed from mother to baby through breast milk. The ability of these components emphasizes the regulate the proliferation and enhancement of intestinal cells as well as the effect of intestinal microbial capacity on the protective role of breast milk in neonatal metabolism and neurodevelopment, intestinal microbial homeostasis and protection against NEC. Underscores the growing research which is studying breastfeeding, enhances the safety value of breast milk in infant nutrition

and protection against inflammatory disorders such as NEC (13).

Discussion and Conclusion

Necrotizing enterocolitis is one of the major problems in narcissistic infants. Numerous factors are involved in the development of the disease. Because NEC is an important cause of mortality and morbidity in narcissistic neonates, prevention of this disease is of particular importance. The most important factor in preventing NEC is preventing premature birth (14). A study by Lars in 2018 on human milk oligosaccharides in the prevention of necrotizing enterocolitis found that premature infants who received breast milk instead of powdered milk were 10 times less likely to develop necrotizing enterocolitis (NEC) which is one of the most common and destructive intestinal disorders that affect up to 10% of all very low birth weight infants (15). Also a study conducted by Jinghai Zhu et al. in 2021 on the effects of exosomes derived from early and term human milk elucidated their lipid expression profiles. The study also found that human milk can prevent necrotizing enterocolitis (NEC). Human milk is rich in carrier exosomes that participate in intercellular communication (16). In a study by Bakuan Jang et al in 2020 on the protective effects of different doses of human milk on necrotic enterocolitis in infants, they found that human milk was effective in preventing NEC and that there was a negative correlation between human milk absorption and NEC incidence. The meta-analysis showed that premature infants fed human milk had a lower incidence of NEC than infants who were formula-fed, especially those who were primarily or entirely breastfed. In the future, more RCTs are needed to provide conclusions on strength and capacity (17).

Also, many studies confirming the above studies have shown that the use of breast milk instead of powdered milk can have a positive effect on reducing the disease of premature infants admitted to the NICU (22-28). In a 2022 study by Roberta Samut et al. On the association between human milk enhancers and necrotic enterocolitis in preterm infants, the results of this study appear to be irrefutable evidence of a link between human milk and milk enhancers and reduce the risk of necrotic enterocolitis in low birth weight, very low birth weight and very low birth weight compared to formula. The strength of this evidence can be considered moderate to high (23). Based on the above findings, most studies have shown that breastfeeding is very important for the health of infants, because it is a method of nutrition that naturally promotes the health of infants and mothers in various ways, from various diseases. One of the most important is to prevent necrotizing enterocolitis and even death in childhood. , And will be well reflected in the future in the form of prevention of several common diseases in adult life.

Resources

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European Heart J* 2018;39(33):3021-104.
2. Griendling K. K., Camargo, L. L., Rios, F. J., Alves-Lopes, R., Montezano, A. C., & Touyz, R. M. (2021). Oxidative stress and hypertension. *Circulation Research*, 128(7), 993-1020.
3. Patel, A. L., & Kim, J. H. (2018, February). Human milk and necrotizing enterocolitis. In *Seminars in Pediatric Surgery* (Vol. 27, No. 1, pp. 34-38). WB Saunders.]
4. Shoji, H.; Shimizu, T.; Shinohara, K.; Oguchi, S.; Shiga, S.; Yamashiro, Y. Suppressive effects of breast milk on oxidative DNA damage in very low birthweight infants. *Arch. Dis. Child Fetal. Neonatal.* Edit. 2004, 89, F136–F138.
5. Henry, M. C., & Moss, R. L.(2009). Necrotizing enterocolitis. *Annual review of medicine*, 60, 111-124.]
6. Dominguez, K. M., & Moss, R. L. (2012). Necrotizing enterocolitis. *Clinics in perinatology*, 39(2), 387-401.]
7. Hair, A. B., Peluso, A. M., Hawthorne, K. M., Perez, J., Smith, D. P., Khan, J. Y., ... & Abrams, S. A. (2016). Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. *Breastfeeding Medicine*, 11(2), 70-74.]
8. Zhou, L.; Yoshimura, Y.; Huang, Y.; Suzuki, R.; Yokoyama, M.; Okabe, M.; Shimamura, M. Two independent pathways of maternal cell transmission to offspring: Through placenta during pregnancy and by breast-feeding after birth. *Immunology* 2000, 101, 570–580.
9. Lewis, E.D.; Richard, C.; Larsen, B.M.; Field, C.J. The importance of human milk for immunity in preterm infants. *Clin. Perinatol.* 2017, 44, 23–47.
10. Hassiotou, F.; Hepworth, A.R.; Metzger, P.; Tat Lai, C.; Trengove, N.; Hartmann, P.E.; Filgueira, L. Maternal and infant infections stimulate a rapid leukocyte response in breastmilk. *Clin. Transl. Immunol.* 2013, 2, e3.
11. Schanler, R.J. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely

- premature infants. *Pediatrics* 2005, 116, 400–406.
12. Bravi, F.; Wiens, F.; Decarli, A.; Dal Pont, A.; Agostoni, C.; Ferraroni, M. Impact of maternal nutrition on breast-milk composition: A systematic review. *Am. J. Clin. Nutr.* 2016, 104, 646–662.
 13. Gay, M.C.L.; Koleva, P.T.; Slupsky, C.M.; du Toit, E.; Eggesbo, M.; Johnson, C.C.; Wegienka, G.; Shimojo, N.; Campbell, D.E.; Prescott, S.L.; et al. Worldwide variation in human milk metabolome: Indicators of breast physiology and maternal lifestyle? *Nutrients* 2018, 10, 1151.
 14. Holman RC, Stoll BJ, Curns AT, Yorita KL, Steiner CA, Schonberger LB. Necrotising enterocolitis hospitalisations among neonates in the United States. *Paediatr Perinat Epidemiol.* (2006) 20:498–506. doi: 10.1111/j.1365-3016.2006.00756.x.
 15. Bode, L. (2018). Human milk oligosaccharides in the prevention of necrotizing enterocolitis: a journey from in vitro and in vivo models to mother-infant cohort studies. *Frontiers in pediatrics*, 6, 385.
 16. Chen, W., Chen, X., Qian, Y., Wang, X., Zhou, Y., Yan, X., ... & Han, S. (2021). Lipidomic profiling of human milk derived exosomes and their emerging Roles in the prevention of necrotizing enterocolitis. *Molecular Nutrition & Food Research*, 65(10), 2000845.
 17. Zhang, B., Xiu, W., Dai, Y., & Yang, C. (2020). Protective effects of different doses of human milk on neonatal necrotizing enterocolitis. *Medicine*, 99(37).
 18. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet* (1990) 336:1519–23. doi: 10.1016/0140-6736(90)93304-8.
 19. Meinen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *J Perinatol.* (2009) 29:57–62. doi: 10.1038/jp.2008.117.
 20. Quigley MA, Henderson G, Anthony MY, McGuire W. Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev.* (2007) 4:CD002971. doi: 10.1002/14651858.CD002971.pub2.
 21. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawöger R, Kiechl-Kohlendorfer U, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr.* (2010) 156:562–7.e1. doi: 10.1016/j.jpeds.2009.10.040.
 22. Kunz C, Rudloff S, Baier W, Klein N, Strobel S. Oligosaccharides in human milk: structural, functional, and metabolic aspects. *Annu Rev Nutr.* (2000) 20:699–722. doi: 10.1146/annurev.nutr.20.1.699
 23. Magro, S., Cini, A., & Sammut, R. (2022). The association between human milk and human milk fortifiers and necrotising enterocolitis in preterm infants: A review. *Journal of Neonatal Nursing*.