Published online: 2020-03-24

Childhood-Onset Systemic Lupus Erythematosus: How Is It Associated with Breastfeeding and Mode of Delivery?

Fatemeh Tahghighi[1,2] Banafsheh Sadeghi*[1] Elham Rayzan*[3] Mamak Shariat[4] Fatemeh Nayeri[5] Vahid Ziaee[2,6]

[1] Children's Medical Center, Pediatrics Center of Excellence, Tehran, Iran
[2] Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
[3] Research Center for Immunodeficiencies, Tehran University of Medical Sciences, Tehran, Iran
[4] Maternal, Fetal Neonatal Research Center, Tehran University of Medical Sciences, Tehran, Iran
[5] Breast feeding Research Center, Tehran University of Medical Sciences, Tehran, Iran
[6] Pediatric Rheumatology Research Group, Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence Vahid Ziaee, MD, Division of Pediatric Rheumatology, Children's Medical Center, No. 62 Dr. Gharib Street, Keshavarz Blvd, Tehran 14194, IR Iran (e-mail: ziaee@tums.ac.ir).

J Child Sci 2020;10:e12–e15.

Abstract

Breast milk is a rich source of infants' nutrition and also known to be a source of immune-enhancing molecules. The perinatal factors might have long-term effects on the immune system and also, breastfeeding may have an important role. Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that leads to various organ damages. This idiopathic disease is characterized by high levels of autoantibodies in the circulation. In this case–control study, we have evaluated the association between the breastfeeding and mode of delivery and SLE incidence. In this case–control study, SLE cases were identified in Children's Medical Center and Imam Khomeini Hospital Complex between 2011 and 2017. The control group was chosen from the schools of Tehran and Sari cities. The questionnaires were completed by one of the parents. Seventy-nine cases and 301 controls were included. There was no association among breastfeeding, duration of breastfeeding or exclusive breastfeeding and SLE, the age of diagnosis, or its major organ involvements ($p > 0.05$). The cesarean section (C-section) method was significantly associated with higher disease incidence ($p < 0.005$). The feeding method during infancy had no significant impact on SLE incidence and onset, while the C-section method increased the incident rate.

Keywords
- breastfeeding
- exclusive breastfeeding
- systemic lupus erythematous

Introduction

Breast milk is a rich source of infants' nutrition and also known to be a source of immune enhancing molecules.[1] Breastfeeding has many benefits such as reducing the incidence and severity of diarrhea, respiratory diseases, otitis media, bacterial meningitis, and necrotizing enterocolitis.[2–5] It has been shown that the breast milk is enriched with the immune activating molecules, metabolites, and vitamins that provide protection against various types of infection

* *These authors contributed equally to the manuscript.*

received September 29, 2019
accepted after revision February 1, 2020

DOI https://doi.org/10.1055/s-0040-1705151.
ISSN 2474-5871.

Copyright © 2020 Georg Thieme Verlag KG Stuttgart · New York

License terms

and improve the sufficiency of immune system.[6] Breastmilk is a rich source of antibodies and contributes to the infant's immune system development. Also, it may play an important role in the establishment of the normal gut flora. More than one pathway may play in the mechanism of several autoimmune diseases but all of them are related to the implicit response of the immune system.[7] It is likely that the first months of life may have a long-term effect on the immune system, and the role of breast milk can be noted.[8,9]

Several studies have examined the relationship between breast milk consumption and autoimmune diseases. Studies have shown the relationship between breast milk consumption and fewer autoimmune diseases, including type 1 diabetes, celiac disease, and inflammatory bowel disease.[10–13] On the other hand, recent studies have shown that the mode of delivery has a remarkable impact on immune regulation.[14,15] Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that can affect various organs including the renal, cardiovascular, and nervous system, characterized by the elevated levels of autoantibodies in the circulation.[16]

The purpose of this study is to investigate the relationship between the breast milk consumption and mode of delivery with SLE incidence and onset in children under the age of 16 years.

Materials and Methods

A total number of 118 patients with the diagnosis of SLE were referred to the Children's Medical Center and Imam Khomeini Hospital Complex, Tehran, Iran, from 2011 to 2017, in which 39 patients were older than 16 years of age by the end of 2017 and were excluded based on the study protocol. The remaining 79 patients were enrolled and the age of diagnosis and involvement of vital organs have been studied.

The control group consisted of 301 children under the age of 16 who were referred to the outpatient clinics of Children's Medical Center and schools of Tehran and Sari cities, with no remarkable history of diseases. A full description of the study was given to the parents via phone call and the informed consents were completed prior to filling out the questionnaires by an expert physician.

The inclusion criterion was being under 16 years of age by the end of 2017, in both the groups. SLE diagnosis was confirmed for those who completed at least 4 criteria or more out of the 17 criteria of clinical and immunological criteria in the Systemic Lupus International Collaborating Clinics (SLICC) classification system (at least one clinical criterion and one immunologic criterion and/or lupus nephritis in the presence of positive antinuclear antibody or anti-double-stranded DNA).[17] In the control group, inclusion criteria were: no history of SLE and no history of severe medical conditions leading to hospitalization or frequent visits to the outpatient clinics. Also, diagnosis of all patients was confirmed by a pediatric rheumatologist. Lack of parents' cooperation during data gathering was considered as the exclusion criteria in both groups.

Three major organ involvements, including renal, neurological, and cardiac, were considered as main variables based on SLICC classification system.[17] Perinatal variables were mode of delivery, history of exclusive breastfeeding, duration of breastfeeding, and birth weight.

Data Analysis

All of the data were analyzed using *IBM* SPSS 23.0 software (IBM, Armonk, New York, United States). To examine the relationship between qualitative variables, "*Pearson's chi-squared*" test (χ^2) was performed. To check the normal distribution of data, "*Kolmogorov–Smirnov*" and "*Shapiro–Wilk*" tests were used. Regarding the non-normal distribution of data in this study, the nonparametric "*Mann–Whitney*" U test was performed.

Sample Size Calculation

In a study by Simard et al in 2008, the history of exclusive breastfeeding during infancy up to 6 months of age was 5% among patients with established SLE; while in an Iranian study in 2015, this prevalence was estimated up to 17%. Based on these studies, the sample size was calculated.[18]

Results

The study population consisted of 79 cases in the patients' group with the sex ratio of 63 females to 16 males and 301 participants in the control group (64.8 females vs. 35.2% males). All of the participants were between 1 and 16 years of age.

The prevalence of breastfeeding among the patients and the control group was 92.4 and 93.7%, respectively, while the prevalence of exclusive breastfeeding had decreased down to 34.2% in the patients' group versus 42.9% in the control group. The mean duration of breastfeeding within two groups and the mean age of diagnosis in the exclusive/nonexclusive breastfed children were devoid of statistical significance.

The prevalence of systemic side effects of SLE based on the breastfeeding and exclusive breastfeeding status is illustrated in ►**Table 1**. The mean differences between groups were not significant.

The investigation showed a remarkable significance between the delivery method and disease occurrence. In patients' group, 54.5% (43/79 patients) of the infants were born by cesarean section (C-section), but in healthy group this rate was 28.6% (86/301 subjects). Thus, those born with the C-section method were associated with the higher prevalence of childhood-onset SLE ($p < 0.001$).

The mean duration of breastfeeding in the control and patients' group was 17.147.8 months versus 18.548.14 months, respectively, which was not statistically significant. The mean age at diagnosis in children with breastfeeding history was 9.315.94 years, which was higher than the non-breast milk group with an average of 8.165.9 years; however, this difference was also devoid of statistical significance. The

Table 1 The main clinical side effects of childhood-onset SLE based on the breastfeeding status

	Overall prevalence (%)	Nonbreastfeeding (%)	Breastfeeding (%)	Exclusive breastfeeding (%)	*p*-Value
Renal involvement	53.2	50	53.4	48.1	0.6[a]
Neurological involvement	38	16.7	39.7	48.1	0.2[a]
Cardiac involvement	10.1	16.7	9.6	3.7	0.5[a]

Abbreviation: SLE, systemic lupus erythematosus.
[a]Not significant.

comparison of mean age at diagnosis in children who had a 6-month history of exclusive breastfeeding was following the same order between both the study groups. Birth weight and other evaluated perinatal factors were not significantly associated with childhood-onset SLE.

Discussion

In this study, the relationship between breast milk consumption, exclusive breastfeeding, and duration of lactation with the incidence and onset of SLE has been studied in a group of children younger than 16 years of age. Involvement of vital organs has been evaluated as well.

Several studies have been conducted to investigate the effect of breast milk consumption on the occurrence of autoimmune disease such as type 1 diabetes, celiac disease, and inflammatory bowel disease.[10] Some studies have found conflicting results while seeking the relationship between breastfeeding and juvenile idiopathic arthritis (JIA).[19–21] On the other hand, a few studies have been done on the role of breast milk in SLE, especially on the childhood-onset subgroup. This study has investigated this relation for the first time.

In this study, the prevalence of breast milk consumption and exclusive breastfeeding was higher in the control group, but this difference was not statistically significant. Harvard's cohort study on the adulthood SLE also had a similar outcome.[18]

Although there were no significant differences, the frequency of breastfeeding and exclusive use of breast milk in the control group was higher than the patient group, and also in patients with a history of breastfeeding and exclusive use of breast milk, the mean age of disease occurrence was higher. These differences could be clinically important.

In our study, the prevalence of renal and neurological involvement among patients' group with a positive history of breastfeeding was higher than those who did not breastfeed their children. However, the prevalence of cardiac involvement in the breastfed was less than in the non-breastfed children. This heterogeneity is likely to be the result of small sample size, especially in the nonbreastfed arm. Although neither of these comparisons was statistically significant, the association of breastfeeding and involvement of vital organs in the SLE patients could not be excluded. Moreover, in a study on the association between breastfeeding and JIA in 2016, breastfeeding had reduced the disease severity, but there was not any confirmed data about SLE presentations to be influenced by the feeding methods during infancy.[19] A comparison also was made to investigate the relationship between exclusive breastfeeding and SLE complications, but as it is shown in ►**Table 1**, these differences were devoid of statistical significance.

The most important finding in this article was the positive association between the delivery method and the incidence of disease. Therefore, the incidence of childhood SLE was significantly higher in the C-section method in comparison to normal vaginal delivery (NVD). However, there was no positive significance among the delivery method and other clinical factors, for instance, the age at diagnosis and presentations. The probable hypothesis could be the impact of C-section on the formation of newborn's gut flora. Meanwhile, it has been suggested that the primary flora formation of the gut is a determinant factor for improving autoimmune diseases via dysregulating immune modulators.[14,15] The CD4+ T cells dysregulation may play a pivotal role as the underlying molecular mechanism in SLE pathogenesis.[22] On the other hand, presence of an undetermined genetic or environmental factor could commonly affect the mode of delivery and predisposition to childhood-onset SLE.

Based on recent studies, the impact of birth weight on the incidence of childhood-onset SLE is controversial. In the present study, the same as a Swedish one, high birth weight had no significant influence on the disease onset and incidence.[23] However, some other studies have investigated that high birth weight is positively correlated with adulthood SLE incidence.[18]

There were some limitations in the present study that need to be addressed in the future investigations. The most important limitation was the unavailability of appropriate data on the indication of choosing C-section over NVD. Therefore, there would be several cases of elective C-sections among the case group without any common genetic or environmental predispositions to specific diseases. The sample size has to be bigger in each group, especially in the nonbreastfed arm. Some parents did not remember the details about their children feeding status. Therefore, it is suggested to use the patients' documented health and growth information to avoid data loss.

This observation suggests that the mode of delivery can affect the incidence of childhood-onset SLE. However, more researches are recommended to assess the exact mechanisms and details.

Conflict of Interest
None declared.

Acknowledgments
This research was part of a General Physician thesis (of Dr. B. Sadeghi) and it was approved and supported by Vice-Chancellor for Research of School of Medicine, Tehran University of Medical Sciences. The authors would like to thank the cooperative staff of the Children's Medical Center and Imam Khomeini Hospital Complex as well as the children and their parents for all the support.

References

1 Vieira Borba V, Sharif K, Shoenfeld Y. Breastfeeding and autoimmunity: programing health from the beginning. Am J Reprod Immunol 2018;79(01):e12778
2 Lodge CJ, Bowatte G, Matheson MC, Dharmage SC. The role of breastfeeding in childhood otitis media. Curr Allergy Asthma Rep 2016;16(09):68
3 Santos FS, Santos FCS, Santos LH, Leite AM, Mello DF. Breastfeeding and protection against diarrhea: an integrative review of literature. Einstein (Sao Paulo) 2015;13(03):435–440
4 Silfverdal SA, Bodin L, Olcén P. Protective effect of breastfeeding: an ecologic study of Haemophilus influenzae meningitis and breastfeeding in a Swedish population. Int J Epidemiol 1999;28 (01):152–156
5 Vereen S, Gebretsadik T, Hartert TV, et al. Association between breast-feeding and severity of acute viral respiratory tract infection. Pediatr Infect Dis J 2014;33(09):986–988
6 Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. Early Hum Dev 2015;91(11):629–635
7 Theofilopoulos AN, Kono DH, Baccala R. The multiple pathways to autoimmunity. Nat Immunol 2017;18(07):716–724
8 Hosea Blewett HJ, Cicalo MC, Holland CD, Field CJ. The immunological components of human milk. Adv Food Nutr Res 2008; 54:45–80
9 Rautava S. Early microbial contact, the breast milk microbiome and child health. J Dev Orig Health Dis 2016;7(01):5–14
10 Cunningham AS, Jelliffe DB, Jelliffe EF. Breast-feeding and health in the 1980s: a global epidemiologic review. J Pediatr 1991;118 (05):659–666
11 Akobeng AK, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. Arch Dis Child 2006;91(01): 39–43
12 Malcova H, Sumnik Z, Drevinek P, Venhacova J, Lebl J, Cinek O. Absence of breast-feeding is associated with the risk of type 1 diabetes: a case-control study in a population with rapidly increasing incidence. Eur J Pediatr 2006;165(02):114–119
13 Xu L, Lochhead P, Ko Y, Claggett B, Leong RW, Ananthakrishnan AN. Systematic review with meta-analysis: breastfeeding and the risk of Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther 2017;46(09):780–789
14 Hansen CH, Andersen LS, Krych L, et al. Mode of delivery shapes gut colonization pattern and modulates regulatory immunity in mice. J Immunol 2014;193(03):1213–1222
15 Zachariassen LF, Krych L, Rasmussen SH, et al. Cesarean section induces microbiota-regulated immune disturbances in C57BL/6 mice. J Immunol 2019;202(01):142–150
16 Weidmann CE, Wallace DJ, Peter JB, Knight PJ, Bear MB, Klinenberg JR. Studies of IgG, IgM and IgA antiphospholipid antibody isotypes in systemic lupus erythematosus. J Rheumatol 1988;15(01): 74–79
17 Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012;64(08):2677–2686
18 Simard JF, Karlson EW, Costenbader KH, et al. Perinatal factors and adult-onset lupus. Arthritis Rheum 2008;59(08):1155–1161
19 Hyrich KL, Baildam E, Pickford H, et al. Influence of past breast feeding on pattern and severity of presentation of juvenile idiopathic arthritis. Arch Dis Child 2016;101(04): 348–351
20 Rosenberg AM. Evaluation of associations between breast feeding and subsequent development of juvenile rheumatoid arthritis. J Rheumatol 1996;23(06):1080–1082
21 Mason T, Rabinovich CE, Fredrickson DD, et al. Breast feeding and the development of juvenile rheumatoid arthritis. J Rheumatol 1995;22(06):1166–1170
22 Reininger L, Santiago ML, Takahashi S, Fossati L, Izui S. T helper cell subsets in the pathogenesis of systemic lupus erythematosus. Ann Med Interne (Paris) 1996;147(07):467–471
23 Arkema EV, Simard JF. Perinatal risk factors for future SLE: a population-based nested case-control study. Lupus 2015;24(08): 869–874