J Surg Med. 2020;4(11):1013-1017.
DOI: 10.28982/josam.826501

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of potential early life risk factors for ulcerative colitis

Ülseratif kolit için potansiyel erken yaşam risk faktörlerinin değerlendirilmesi

Yasemin Gökden [1], Deniz Öğütmen Koç [2]

[1] University of Health Sciences Cemil Tascıoglu City Hospital, Department of Gastroenterology Istanbul, Turkey
[2] University of Health Sciences Gaziosmanpasa Training and Research Hospital, Department of Gastroenterology, Istanbul, Turkey

ORCID ID of the author(s)
YG: 0000-0001-6767-3072
DÖK: 0000-0003-2738-625X

Corresponding author / Sorumlu yazar:
Yasemin Gökden
Address / Adres: Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi, Gastroenteroloji Kliniği, İstanbul, Türkiye
E-mail: yasemingokden@hotmail.com

Ethics Committee Approval: The study was approved by the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 20.10.2020, decision no: 409). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi Etik Kurulu tarafından onaylandı (tarih: 20.10.2020, karar no: 409). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

Abstract

Aim: It has been suggested that early life factors may affect the risk of inflammatory bowel disease by affecting the gut microbiome. Delivery type, breast milk, and parental smoking are the most important environmental factors. There are limited studies on the effects of these factors on the location of the disease and age at diagnosis. In addition, the effects of these factors on medical treatments and bowel involvement are unknown. We examined the relationship between potential early-life risk factors experienced in the first years of life and ulcerative colitis (UC).

Material and Method: This study is a prospective case-control study. Sixty-nine UC patients were compared with 44 age- and sex-matched healthy controls (HC). We investigated delivery type, breastfeeding, maternal age at birth, and parents' smoking status, which may be potential early-life risk factors. Our analysis involved the relationship of these potential factors with the age at diagnosis and medical treatments in UC patients.

Results: UC and HC groups were compared in terms of delivery type, breastfeeding, and parents' smoking status: There was no statistical difference between the groups. In terms of the duration of breastfeeding, we found that 6-12 months of breastfeeding was lower in the UC group (P=0.046). In addition, the age at diagnosis of the disease was lower in UC patients who were not breastfed and whose mothers smoked (P=0.031, P=0.016, respectively).

Conclusions: The duration of breastfeeding is important for the development of UC. We recommend breastfeeding for longer than six months to prevent UC. Maternal smoking cessation has a protective role in the risk of early-onset UC.

Keywords: Ulcerative colitis, Early life factors, Breastfeeding, Delivery

Öz

Amaç: Erken yaşam faktörlerinin bağırsak mikrobiyomunu etkileyerek iltihaplı bağırsak hastalığı riskini etkileyebileceği öne sürülmüştür. Doğum şekli, anne sütü ve ebeveynlerin sigara içmesi en önemli çevresel faktörlerdir. Bu faktörlerin hastalığın yeri ve tanı anındaki yaş üzerindeki etkileri konusunda sınırlı sayıda çalışma bulunmaktadır. Ayrıca bu faktörlerin medikal tedavilere ve barsak tutulum yerine etkisi de bilinmemektedir. Yaşamın ilk yıllarında yaşanan potansiyel erken yaşam risk faktörleri ile ülseratif kolit (ÜK) arasındaki ilişkiyi inceledik.

Yöntemler: Bu çalışma prospektif bir vaka kontrol çalışmasıdır. Atmış dokuz ÜK hastası yaş ve cinsiyet bakımından benzer 44 sağlıklı kontrol ile karşılaştırıldı. Potansiyel erken yaşam risk faktörü olabilecek doğum şekli, anne sütü ile beslenme, anne doğum yaşı, anne ve baba sigara kullanım durumları araştırıldı. ÜK hastalarında bu potansiyel faktörlerin hastalık tanı yaşı, medikal tedavilerle ilişkisi incelendi.

Bulgular: ÜK ve kontrol grubu, doğum şekilleri, anne sütü ile beslenme, anne-baba sigara kullanma durumları bakımından karşılaştırıldığında gruplar arasında istatistiksel farklılık izlenmedi. Anne sütü alma süreleri bakımından karşılaştırıldığında ise 6-12 ay arası anne sütü alanlar, ÜK grubunda daha düşük saptanmıştır (P=0,046). Ayrıca anne sütü almayan ÜK hastaları ile annesi sigara kullanan ÜK hastalarının hastalık tanı yaşları daha düşük bulunmuştur (sırasıyla: P=0,031, P=0,016).

Sonuçlar: ÜK gelişimi açısından emzirmenin süresi önemlidir. ÜK'den korunmak için 6 aydan daha uzun anne sütü ile beslenme önermekteyiz. Erken başlangıçlı ÜK riski açısından annenin sigarayı bırakmasının koruyucu rolü vardır.

Anahtar kelimeler: Ülseratif kolit, Erken yaşam faktörleri, Anne sütü, Doğum

How to cite/Atıf için: Gökden Y, Koç DÖ. Evaluation of potential early life risk factors for ulcerative colitis. J Surg Med. 2020;4(11):1013-1017.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of inflammatory bowel disease (IBD), a chronic inflammatory disease of the gastrointestinal system of unknown cause. Its etiology is not yet fully known; however, it is thought to be caused by an exaggerated immunological response triggered by environmental and genetic factors [1]. The perinatal period is the period of first exposure to many antigenic stimuli. During this period, many factors act as markers by affecting the composition of the gut microbiome and its composition [2]. Increasing evidence suggests that early-life factors are determinants of a person's health and disease status in their future life. There are also epidemiological studies reporting that perinatal or childhood events play a role in the etiology of IBD [3,4].

It is thought that some factors affecting the gut microbiome in the perinatal period and the first years of life may also be related to immune-mediated diseases, including UC [5,6,7]. However, the triggers to develop UC remain unknown.

The present study investigated whether critical events experienced at birth or in the first years of life and those thought to cause changes in the gut microbiome in individuals, such as delivery type, breastfeeding, and maternal age at birth could be a risk for UC. Our evaluation included the relationship of these factors with the age at UC diagnosis, the site of intestinal involvement, and medical treatments. Considering that parents' smoking might cause passive nicotine exposure in the first years of life, whether this is a risk for UC and affects the age of diagnosis and medical treatments were also included in the analysis.

Materials and methods

Ethics committee approval was obtained for this prospective case-control study. In this study, informed consent was obtained from all participants whose data could be analyzed and published for scientific purposes. A detailed questionnaire was then administered by telephone. The study included patients >18 years of age, with definite endoscopic, pathological, and radiological diagnosis of UC, followed at the Prof. Dr. Cemil Taşcıoğlu Gastroenterology outpatient clinic. Those <18 years of age, with incomplete answers, and an unclear diagnosis of UC were excluded.

Healthy controls (HC) matching in age and gender were also included in the study. They were selected among those who visited our hospital for their routine check-up and did not have any known diseases, malignancy, or drug history. UC and HC groups were asked about the maternal age of birth, type of delivery (vaginal or cesarean section), parental smoking, and whether they were breastfed, and if so, its duration (0-6 months, 6-12 months, and >12 months). In addition, from the hospital records of UC patients, the year of disease diagnosis, medical treatment, and disease locations in the intestine were recorded. Endoscopic involvement sites were grouped as rectal, distal, left colon, and pancolitis.

Statistical analysis

Number Cruncher Statistical System (NCSS) program was used for statistical analysis. The study data were analyzed using descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum). The suitability of quantitative data to normal distribution was tested by the Shapiro-Wilk test and graphical analyses. Student's t-test was used for comparing two groups of normally distributed quantitative variables and the Mann-Whitney U test for comparisons of quantitative variables that did not show normal distribution. The Kruskal-Wallis test was used to compare more than two groups of quantitative variables that did not show normal distribution. Pearson's chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton exact test were used to compare qualitative data. The Pearson correlation coefficient was used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $P<0.05$.

Results

In total, 113 subjects (69 UC patients and 44 HCs) between the ages of 18–72 years [59 females (52.2%) and 54 males (47.6%)] were included in the study. UC and HC groups were similar in terms of average age and gender ratios.

UC and HC groups were compared regarding the type of delivery, breastfeeding (no or yes), and the parents' smoking status: there was no statistical difference between the groups. When the breastfed UC and HC groups were compared in terms of the duration of breastfeeding, the number of those who received breast milk between 6-12 months was lower in the UC group ($P=0.046$). Maternal age at birth was also significantly lower in the UC group than in the HC group ($P=0.032$) (Table 1).

Table 1: Evaluation of descriptive features according to groups

		Total	UC (n=69)	HC (n=44)	*P*-value
Age	Min-Max (Median)	18-72 (38)	18-72 (37)	18-67 (41)	[a]0.627
	mean(Sd)	39.23(13.46)	39.72(13.26)	38.45(13.90)	
Gender	Male	54 (47.80)	35 (50.7)	19 (43.2)	[b]0.434
	Female	59 (52.2)	34 (49.3)	25 (56.8)	
BMI (kg/m^2)	Min-Max (Median)	17.3-36.3 (24.7)	17.3-36.3 (24.6)	17.6-30.1 (25.2)	[a]0.768
	mean(Sd)	24.64(3.91)	24.73(4.33)	24.51(3.20)	
Father's smoking	No	47 (41.6)	26 (37.7)	21 (47.7)	[b]0.291
	Yes	66 (58.4)	43 (62.3)	23 (52.3)	
Mothers' smoking	No	94 (83.2)	56 (81.2)	38 (86.4)	[b]0.471
	Yes	19 (16.8)	13 (18.8)	6 (13.6)	
Delivery Type	Vaginal	106 (93.8)	65 (94.2)	41 (93.2)	[c]1.000
	Cesarean section	7 (6.2)	4 (5.8)	3 (6.8)	
Breastfeeding	No	17 (15.0)	12 (17.4)	5 (11.4)	[b]0.382
	Yes	96 (85.0)	57 (82.6)	39 (88.6)	
Breastfeeding time	0-6 mount	19 (19.8)	15 (26.3)	4 (10.3)	[b]0.046*
	6-12 mount	24 (25.0)	10 (17.5)	14 (35.9)	
	>12 mount	53 (55.2)	32 (56.1)	21 (53.8)	
Maternal age at birth	Min-Max (Median)	14-44 (25)	14-42 (24)	19-44 (26)	[a]0.032*
	mean(Sd)	25.83(6.35)	24.81(6.13)	27.43(6.41)	

[a] Student-t Test, [b] Pearson Chi-Square Test, [c] Fisher's Exact Test, * $P<0.05$, UC: ulcerative colitis, HC: healthy controls

The age at the diagnosis of the disease ranged from 11 to 64 years, with an average age of 34.28 ± 12.52 in the UC group. The disease involvement sites were as follows: Rectal in 10.1% (n=7), distal in 26.1% (n=18), left colon in 20.3% (n=14), and pancolitis in 43.5% (n=30). In the same group, 71% (n=49) of the patients received single medication, 29% (n=20) received two medications or more: 95.7% (n=66) received mesalazine, 13% (n=9), azathioprine, 11.6% (n=8), anti-TNF, and 11.6% (n=8) received steroid therapy.

When the UC group is evaluated in terms of age at the time of diagnosis, no statistical relationship was found in terms

of gender, maternal age at birth, mode of delivery, father's smoking, and medical treatments (Table 2).

The UC diagnosis ages of patients whose mothers smoked were significantly lower than those whose mothers did not smoke (P=0.016). The diagnosis ages were also significantly lower in UC patients who were not breastfed than those who were (P=0.031) (Figure 1).

Table 2: Evaluations regarding the age at diagnosis of the ulcerative colitis patient

		Patient Diagnosis Age		
		r	*P*-value	
BMI (kg/m^2)		0.387	0.001**	
Maternal age at birth		0.173	0.155	
		Min-Max (Median)	Mean(Sd)	*P*-value
Gender	Male (n=35)	15-64 (34)	36.66(12.21)	[a]0.110
	Famale (n=34)	11-59 (30)	31.82(12.54)	
Father's smoking	No (n=26)	15-64 (34)	36.31(12.77)	[a]0.298
	Yes (n=43)	11-59 (32)	33.05(12.36)	
Mothers' smoking	No (n=56)	15-64 (34.5)	36.02(12.43)	[d]0.016*
	Yes(n=13)	11-50 (26)	26.77(10.26)	
Mesalazine	No (n=3)	20-43 (38)	33.67(12,1)	[d]0.930
	Yes (n=66)	11-64 (32.5)	34.30(12.63)	
Azathioprine	No (n=60)	11-64 (33.5)	35.12(12.44)	[d]0.130
	Yes (n=9)	14-54 (28)	28.67(12.3)	
Anti-TNF	No (n=61)	14-64 (33)	34.31(12.31)	[d]0.955
	Yes (n=8)	11-49 (36.5)	34.00(14.97)	
Steroid	No (n=61)	11-64 (33)	34.38(12,43)	[d]0.837
	Yes(n=8)	14-54 (31.5)	33.5(14.08)	
	Vaginal (n=65)	14-64 (33)	34.89(12.32)	[d]0.182
Delivery Type	Cesarean (n=4)	11-37 (24.5)	24.25(13.15)	
	No (n=12)	11-55 (26)	27.42(13.68)	[d]0.031*
Breastfeeding	Yes (n=57)	15-64 (34)	35.72(11.9)	
	0-6 mount (n=15)	21-64 (37)	37.07(11.83)	[e]0.638
Breastfeeding time	6-12 mount(n=10)	28-55 (33)	37.70(9.89)	
	>12 mount(n=32)	15-59 (33)	34.47(12.66)	

[a] Student-t Test, [d] Mann Whitney U Test, [e] Kruskal Wallis Test, * P<0.05, ** P<0.01, r= Pearson Correlation Coefficient

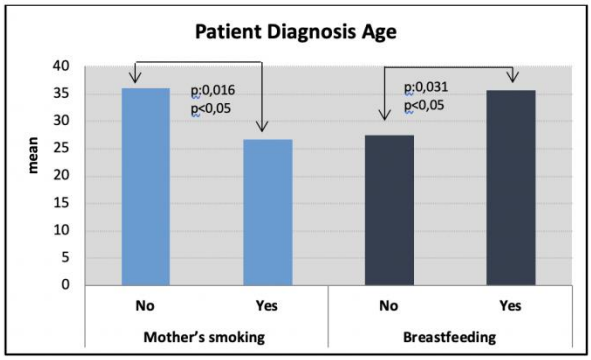

Figure 1: Age of diagnosis of ulcerative colitis according to mother's smoking and breastfeeding

There was no statistically significant difference in the disease involvement site and anti-TNF use in the UC group in terms of age, gender, parental smoking, type of delivery, breastfeeding and its duration, and maternal birth age (Table 3, 4).

Table 3: Evaluation according to disease degree in patients with ulcerative colitis

		Disease location				
		Proctitis (n=7)	Distal (18)	left side (n=14)	Pancolitis (n=30)	*P*-value
Age	Min-Max (Median)	27-60 (40)	18-72 (37.5)	22-70 (36)	18-64 (36)	[e]0.745
	Mean(Sd)	43.29(11.19)	40.17(14.77)	39.86(13.84)	38.57(12.95)	
Gender	Male	3 (42.9)	11 (61.1)	9 (64.3)	12 (40.0)	[f]0.363
	Female	4 (57,1)	7 (38.9)	5 (35.7)	18 (60.0)	
BMI (kg/m^2)	Min-Max (Median)	19.7-35.2 (25.4)	18.9-36.3(24.4)	17.3-29.6(23.8)	18.4-33.7 (25.2)	[e]0.916
	Mean(Sd)	26.05(5.55)	25.22(5.33)	24.04(3.81)	24.45(3.67)	
Father's smoking	No	2 (28.6)	8 (44.4)	6 (42.9)	10 (33.3)	[f]0.822
	Yes	5 (71.4)	10 (55.6)	8 (57.1)	20 (66.7)	
Mothers' smoking	No	6 (85.7)	15 (83.3)	11 (78.6)	24 (80.0)	[f]1.000
	Yes	1 (14.3)	3 (16.7)	3 (21.4)	6 (20.0)	
Mesalazine	No	0 (0.0)	1 (5.6)	0 (0.0)	2 (6.7)	[f]1.000
	Yes	7 (100.0)	17 (94.4)	14 (100.0)	28 (93.3)	
Azathioprine	No	7 (100.0)	16 (88.9)	13 (92.9)	24 (80.0)	[f]0.655
	Yes	0 (0.0)	2 (11.1)	1 (7.1)	6 (20.0)	
Anti-TNF	No	7 (100.0)	16 (88.9)	12 (85.7)	26 (86.7)	[f]0.901
	Yes	0 (0.0)	2 (11.1)	2 (14.3)	4 (13.3)	
Steroid	No	7 (100.0)	18 (100.0)	13 (92.9)	23 (76.7)	[f]0.072
	Yes	0 (0.0)	0 (0.0)	1 (7.1)	7 (23.3)	
Delivery Type	Vaginal	6 (85.7)	17 (94.4)	13 (92.9)	29 (96.7)	[f]0.505
	Cesarean	1 (14.3)	1 (5.6)	1 (7.1)	1 (3.3)	
Breastfeeding	No	0 (0.0)	4 (22.2)	3 (21.4)	5 (16.7)	[f]0.647
	Yes	7 (100.0)	14 (77.8)	11 (78.6)	25 (83.3)	
Breastfeeding time	0-6 mount	1 (14.3)	2 (14.3)	4 (36.4)	8 (32.0)	[f]0.811
	6-12 mount	1 (14.3)	3 (21.4)	1 (9.1)	5 (20.0)	
	>12 mount	5 (71.4)	9 (64.3)	6 (54.5)	13 (48.0)	
Maternal age at birth	Min-Max (Median)	21-40 (25)	14-36 (22)	19-30 (23.5)	16-42 (23.5)	[e]0.570
	Mean(Sd)	27.14(6.01)	23.83(6.22)	24.29(3.54)	25.10(7.08)	

[e] Kruskal Wallis Test, [f] Fisher Freeman Halton Test

Table 4: Comparisons for Anti TNF Use in Ulcerative Colitis Patients

		Anti- TNF		
		No (n=61)	Yes (n=8)	*P*-value
Age	Min-Max(Median)	18-72 (37)	18-58 (40.5)	[d]0.910
	Mean(Sd)	39.79(13.18)	39.25(14.72)	
Gender	Male	33 (54.1)	2 (25.0)	[c]0.151
	Female	28 (45.9)	6 (75.0)	
BMI (kg/m^2)	Min-Max (Median)	17.3-36.3 (25.1)	18.9-36.3 (22.5)	[d]0.494
	Mean(Sd)	24.78(4.21)	24.27(5.40)	
Father's smoking	No	21 (34.4)	5 (62.5)	[c]0.143
	Yes	40 (65.6)	3 (37.5)	
Mothers' smoking	No	49 (80.3)	7 (87.5)	[c]1.000
	Yes	12 (19.7)	1 (12.5)	
Delivery Type	Vaginal	59 (96.7)	6 (75.0)	[c]0.063
	Cesarean	2 (3.3)	2 (25.0)	
Breastfeeding	No	10 (16.4)	2 (25.0)	[c]0.621
	Yes	51 (83.6)	6 (75.0)	
Breastfeeding time	0-6 ay	13 (14.3)	2 (33.3)	[f]0.852
	6-12 ay	9 (17.6)	1 (16.7)	
	>12 ay	29 (56.9)	3 (50.0)	
Maternal age at birth	Min-Max(Median)	14-42 (24)	18-38 (24)	[d]0.403
	Mean(Sd)	24.61(6.12)	26.37(6.36)	

[b] Pearson Chi-Square Test, [c] Fisher's Exact Test, [d] Mann Whitney U Test, [f] Fisher Freeman Halton Test

Discussion

Critical events experienced at birth or in the first year of life can increase IBD risk by causing changes in the gut microbiome. Delivery type and breastfeeding are among the critical factors that can affect the gut microbiome. Exposure to bacteria from both the mother and the environment is decisive on an infant's intestinal flora. Breast milk is one of the earliest environmental factors a baby is exposed to. The microbiota of breastfed babies contains higher concentrations of bifidobacteria and less anaerobic bacteria than that of bottle-fed babies. Besides, fecal flora can change up to the age of 1-2 years [8-10].

The relationship between breastfeeding and UC is complex. A study by Klement et al. [7] reported that breastfeeding is protective for UC. Again, a systematic review and meta-analysis showed a strong inverse relationship between breastfeeding in infancy and the development of pediatric- and adult-onset IBD. One of the most important results from this analysis is the time-response effect of breastfeeding on both CD and UC development. While even three months of breastfeeding

is protective compared to no breastfeeding at all, it is emphasized that it has an even greater effect when occurred for >12 months [11].

There are also studies reporting that breastfeeding does not affect the development of UC and CD [12-15]. In these studies, the mean breastfeeding duration is generally short or its relationship with duration has not been investigated. The common feature of the studies advocating the protective effect of breast milk on UC and CD is the emphasis on breastfeeding for longer than three months [16].

It was concluded in our study that the duration of breastfeeding is important to prevent UC. While there was no difference between UC and HC regarding breastfeeding during the first six months, breastfeeding between 6-12 months was lower in the UC group. In addition to the duration of breastfeeding, there is a need for studies on the extent of breastfeeding, that is, the quality of breastfeeding, how much formula and supplementary foods are included in the first years of life, and whether this affects the UC development.

A study on the role of breastfeeding in the development of early-onset IBD showed that breast milk has a protective effect on its development [17]. Similarly, we observed that UC started at an earlier age in patients who did not receive breast milk.

A study by Rigars et al. [18] did not find any relationship between the maternal age at birth, the number of children the mother had, the mother's smoking status, or the birth season and UC. Robert et al [19] found higher CD incidence among mothers >35 years of age. However, they reported that there was no such relationship between UC and maternal age. In our study, the maternal age at birth was lower in UC patients compared to that in HCs. This difference may have resulted from our society's younger age at marriage due to cultural and social differences and having children at earlier ages.

The role of the gut microbiome in the pathogenesis of IBD has not yet been fully defined. However, the specific structure and/or change of the gut microbiome may affect the risk of developing IBD in genetically susceptible individuals. Delivery type is one of the most important risks in early-life and is the main determinant of neonatal intestinal colonization. While babies born vaginally show a microbiota composition closer to their mothers' vaginal and intestinal microbiota, babies born by cesarean section show a microbiota composition similar to maternal skin [20].

According to the delivery method, the IBD risk has not yet been identified. Studies evaluating the relationship between the cesarean section and IBD have conflicting results [12,21]. Bager et al. [21] reported that cesarean delivery caused a moderate increase in the risk of childhood-onset IBD.

A study by Berstein et al. [12] claims that cesarean delivery is not a risk for developing UC. They found that the first years of life are critical for gut microbiome development, and infection and the use of antibiotics during this period are associated with the development of UC in later life. Gomes et al. [15] reported that cesarean section performed under both emergency and elective conditions was not related to an increased UC risk. In our study, there was no statistical difference between UC and HC groups in terms of delivery type. In addition, there was no relationship in terms of delivery type and age at diagnosis, intestinal involvement and medical treatments in UC patients.

Living in rural areas and having spent the first five years of life in rural areas is reportedly a protective factor for UC development [22]. The region where both our UC and HC groups lived is an area receiving high immigration from rural areas. Therefore, it was not possible for us to interpret the results in this respect since there was no group diversity.

It is still unclear what is triggers UC development and gut inflammation. There are also studies on various inflammatory markers, disease behavior and intestinal involvement [23,24]. However, the mystery remains.

Limitations

This study is the first to report that early-life risk factors have no effect on the intestinal involvement sites, medical treatments, and anti-TNF requirement in UC patients. However, our study has some limitations worth mentioning: Potential early-life risk factors in UC patients such as birth weight, preterm birth, infections in infancy, and early exposure to antibiotics were not included in our study. These could affect UC risk. However, we thought that it would not be very reliable to obtain this information by only retrospective questioning of UC patients without official records, which is the reason we chose not to. Another limitation of the study is that childhood vaccines and cow's milk allergy were not included in the study.

Conclusions

In this study, it was emphasized that the mother's passive smoking brings the age of the diagnosis of UC earlier. This reveals the protective role of maternal smoking cessation in the early development of UC. The duration of breastfeeding is important for UC development. We recommend breastfeeding for longer than six months to prevent UC. Additionally, breastfeeding is protective for the risk of early-onset UC.

References

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009;361:2066–78. doi: 10.1056/NEJMra0804647.
2. Hutfless S, Heyman MB, Bayless TM, Abramson O, Lisa J. Herrinton LJ. Prenatal and Perinatal Characteristics Associated with Pediatric-Onset Inflammatory Bowel Disease. Dig Dis Sci (2012) 57:2149–56. doi: 10.1007/s10620-012-2128-1.
3. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504–17. doi: 10.1053/j.gastro.2004.01.063.
4. Marshall JK, Hilsden RJ. Environment and epidemiology of inflammatory bowel diseases. In: Satsangi J, Sutherland RL, eds. Inflammatory bowel diseases. London: Churchill Livingston, 2003:17–28.
5. Metsala J, Kilkkinen A, Kaila M, Tapanainen H, Klaukka T, Gissler M, et al. Perinatal Factors and the Risk of Asthma in Childhood-A Population-based Register Study in Finland. Am J Epidemiol. 2008;168:170-8. doi: 10.1093/aje/kwn105.
6. Ievins R, Roberts SE, Goldacre MJ. Perinatal factors associated with subsequent diabetes mellitus in the child: record linkage study. Diabet Med. 2007;24(6):664-70. doi: 10.1111/j.1464-5491.2007.02147.x.
7. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysi. Am J Clin Nutr. 2004;80(5):1342-52. doi: 10.1093/ajcn/80.5.1342.
8. Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. Acta Paediatr Suppl. 2003;91(441):48–55. doi: 10.1111/j.1651-2227.2003.tb00646.x.
9. Midtvedt AC, Midtvedt T. Production of short chain fatty acids by the intestinal microflora during the first 2 years of human life. J Pediatr Gastroenterol Nutr. 1992;15:395–403. doi: 10.1097/00005176-199211000-00005.
10. Palmer C. Bik EM, Digiulio DB. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5:e177. doi: 10.1371/journal.pbio.0050177.
11. 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 Nov;46(9):780–9. doi: 10.1111/apt.14291.
12. Bernstein CN, Banerjee A, Targownik LE. Cesarean section delivery is not a risk factor for development of inflammatory bowel disease: a population-based Analysis. Clin Gastroenterol Hepatol. 2016;14:50–7. doi: 10.1016/j.cgh.2015.08.005.
13. Khalili H, Ananthakrishnan AN, Higuchi LM, Richter JM, Fuchs CS, Chan AT. Early Life Factors and Risk of Inflammatory Bowel Disease in Adulthood. Inflamm Bowel Dis. 2013 Mar;19(3):542-7. doi: 10.1097/MIB.0b013e31828132f8.
14. Wang Y-F, Ou-yang Q, Xia B, Liu L-N , Gu F, Zhou K-F, et al. Multicenter case-control study of the risk factors for ulcerative colitis in China. World J Gastroenterol. 2013 March 21;19(11):1827-33. doi: 10.3748/wjg.v19.i11.1827.

15.Gomes CF, Narula N, Morão B, Nicola P, Cravo M, Torres J. Mode of delivery does not afect the risk of infammatory bowel disease. Dig Dis Sci. 2020 Mar 21. doi: 10.1007/s10620-020-06204-7.
16.Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. Journal of Gastroenterology and Hepatology. 2010;25:325-33. doi: 10.1111/j.1440-1746.2009.06140.x.
17.Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, Wilson DC. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediatr 2009 Sep;155(3):421-6. doi: 10.1016/j.jpeds.2009.03.017
18.Rigas A, Rigas B, Glassman M, Yen Y, Lan SJ, Petridou E, et al. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. Ann Epidemiol. 1993 Jul;3(4):387-92.
19.Roberts SE, Clare J, Wotton CJ, Williams JG, Griffith M, Goldacre MJ. Perinatal and early life risk factors for inflammatory bowel disease. World J Gastroenterol. 2011 Feb 14;17(6):743-9. doi: 10.1016/1047-2797(93)90066-d.
20.Ley D, Desseyn JL, Mischke M, Knol J, Turck D, Gottrand F. Early-life origin of intestinal infammatory disorders. Nutr Rev. 2017;75:175–87. doi: 10.1093/nutrit/nuw061.
21.Bager P, Simonsen J, Nielsen NM, Frisch M. Cesarean section and ofspring's risk of infammatory bowel disease: a national cohort study. Infamm Bowel Dis. 2012;18:857–62. doi: 10.1002/ibd.21805.
22.Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A. Rural and urban residence during early life is associated with risk of inflammatory bowel disease: a population-based inception and birth cohort study. Am J Gastroenterol. 2017;112:1412–22. doi: 10.1038/ajg.2017.208.
23.Kalyon S, Gökden Y, Oyman F. A new biological marker in inflammatory bowel disease: Pentraxin 3. J Surg Med. 2020;4(10):875-8.
24.Gökden Y, Hot S, Gönen C, Kalyon S, Çetinkaya ZA. The value of adenosine deaminase level in assessing activation of inflammatory bowel disease. J Surg Med. 2020;4(8):654-9. doi: 10.28982/josam.791156.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.