



Year: 2023

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Abstract: BACKGROUND AND AIMS: Childlessness and infertility represent a frequent and important issue in inflammatory bowel disease (IBD) patients. Nevertheless, until now epidemiological data remains scarce. Therefore, main objectives of this study were to evaluate the rate of childlessness and the cumulative probability of reproduction in female and male IBD patients within the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), a large prospective multicenter nationwide cohort. METHODS: Prospectively collected data of SIBDCS was used, comprising more than 3,300 patients with Crohn's disease (CD) and ulcerative colitis (UC). We analyzed the following groups of patients: 1) female IBD patients aged ≥ 40 years and diagnosed before age of 30 years with at least one follow-up, 2) female IBD patients who reported actively trying to conceive, with IBD diagnosed < 35 years and with age at enrolment < 45 years (longitudinal observation), with at least one follow-up, and 3) childless males who actively tried to conceive. RESULTS: A total of 1,412 female patients from the SIBDCS [843 CD, 539 UC, 30 indeterminate colitis (IC)] with available data were included in our analyses. Out of those 184 females (70.1% CD and 29.9% UC) were aged ≥ 40 years and have been diagnosed with IBD before the age of 30 years. Among these, 184 women 32.1% were childless. The portion of childless females (36.4%) was significantly higher in CD vs. UC (36.4% vs. 21.8%; $p=0.026$), equaling a relative risk of childlessness of 1.7 in CD vs. UC. and higher than in the Swiss general population (21%). The mean number of children per female patient was 1.32 (median 1, min 0, max 6), per female with CD 1.12 (median 1, min 0, max 4), per female with UC/IC 1.78 (median 2, min 0, max 6; $P=0.001$). The longitudinal analysis of female IBD patients trying to conceive revealed that one out of two women neither were pregnant nor had born a child five years after first trying to conceive. CONCLUSIONS: The rate of childlessness in females with CD is higher compared to the general Swiss population, whereas it is similar in women with UC. Moreover, the mean number of children is lower in CD than in UC. Females with CD remain more often childless compared to their UC counterparts. Although the exact underlying mechanisms are largely unknown, this discrepancy should alert healthcare professionals treating CD patients to actively address this topic.

DOI: <https://doi.org/10.15403/jgld-5132>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-254249>

Journal Article

Published Version



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Originally published at:

Sulz, Michael Christian; Douberis, Michael; Fournier, Nicolas; Biedermann, Luc; Zeitz, Jonas; Misselwitz, Benjamin; Imthurn, Bruno; Rogler, Gerhard; SIBDCS Group (2023). Childlessness in Patients with Inflammatory Bowel Disease - Data from the Prospective Multi-center Swiss IBD Cohort Study. *Journal of Gastrointestinal and Liver Diseases*, 32(4):460-468.

DOI: <https://doi.org/10.15403/jgld-5132>

Childlessness in Patients with Inflammatory Bowel Disease – Data from the Prospective Multi-center Swiss IBD Cohort Study

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Received: 26.07.2023

Accepted: 24.11.2023

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ABSTRACT

Background & Aims: Childlessness and infertility represent a frequent and important issue in inflammatory bowel disease (IBD) patients. Nevertheless, until now epidemiological data remains scarce. Therefore, main objectives of this study were to evaluate the rate of childlessness and the cumulative probability of reproduction in female and male IBD patients within the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), a large prospective multicenter nationwide cohort.

Methods: Prospectively collected data of SIBDCS was used, comprising more than 3,300 patients with Crohn's disease (CD) and ulcerative colitis (UC). We analyzed the following groups of patients: 1) female IBD patients aged ≥ 40 years and diagnosed before age of 30 years with at least one follow-up, 2) female IBD patients who reported actively trying to conceive, with IBD diagnosed < 35 years and with age at enrolment < 45 years (longitudinal observation), with at least one follow-up, and 3) childless males who actively tried to conceive.

Results: A total of 1,412 female patients from the SIBDCS [843 CD, 539 UC, 30 indeterminate colitis (IC)] with available data were included in our analyses. Out of those 184 females (70.1% CD and 29.9% UC) were aged ≥ 40 years and have been diagnosed with IBD before the age of 30 years. Among these, 184 women 32.1% were childless. The portion of childless females (36.4%) was significantly higher in CD vs. UC (36.4% vs. 21.8%; $p=0.026$), equaling a relative risk of childlessness of 1.7 in CD vs. UC and higher than in the Swiss general population (21%). The mean number of children per female patient was 1.32 (median 1, min 0, max 6), per female with CD 1.12 (median 1, min 0, max 4), per female with UC/IC 1.78 (median 2, min 0, max 6; $P=0.001$). The longitudinal analysis of female IBD patients trying to conceive revealed that one out of two women neither were pregnant nor had born a child five years after first trying to conceive.

Conclusions: The rate of childlessness in females with CD is higher compared to the general Swiss population, whereas it is similar in women with UC. Moreover, the mean number of children is lower in CD than in UC. Females with CD remain more often childless compared to their UC counterparts. Although the exact underlying mechanisms are largely unknown, this discrepancy should alert healthcare professionals treating CD patients to actively address this topic.

Key words: inflammatory bowel disease – IBD – childlessness – infertility – SIBDCS – Crohn's disease – ulcerative colitis.

Abbreviations: CD: Crohn's disease; IBD: inflammatory bowel disease; GSP: General Swiss Population; IC: indeterminate colitis; SIBDCS: Swiss Inflammatory Bowel Disease Cohort Study; UC: ulcerative colitis; VC: voluntary childlessness.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic disabling diseases that typically affect younger patients during reproductive span [1-4]. Therefore, reproductive issues such as fertility and adverse

pregnancy outcomes constitute substantial concerns for many IBD patients, especially women. However, current literature addresses predominantly pregnancy outcomes in IBD or is confined to relatively outdated population-based estimates of fertility [3, 5-7]. Nowadays, there is a general consensus that overall, (i.e. both male and female) fertility is not significantly affected in IBD patients with quiescent disease and absent prior operations [8, 9]. Population based studies in IBD estimate the rate of female infertility between 5–14% in patients in

remission [5, 10], rate which is similar to the one observed in the general population.

Notably, there exists an objective difficulty to quantify infertility and compare the findings derived from different investigations. Among other reasons, this phenomenon can be attributed to the plethora of terms (for instance infertility, reduction of fecundability, involuntary childlessness) being implemented to describe ‘infertility’ in the literature. Tavernier et al. [11] exhibited that a significant (17-44%) reduction of fertility in females with Crohn’s disease (CD) compared to controls was linked to voluntary childlessness (VC), whereas there was no evidence of pathological causes of infertility [11]. The reasons accountable for VC are multiple, including fear of disease relapse, IBD inheritance, inability or reluctance to care for the child, additional stress the birth of a child might accompany, or drug interactions during pregnancy [1, 12, 13]. Voluntary childlessness has been also previously associated with lower educational levels [14]. In summary, the issue of ‘infertility’ is rather complex, implicates various aspects and represents a nebulous term. In contrast, childlessness is an entirely transparent and measurable parameter. Therefore, in our study we focused on childlessness. The main objective of our study was to evaluate the rate of childlessness in females within the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS), a large prospective multi-center IBD cohort, and to assess the cumulative probability of pregnancy or maternity/paternity.

METHODS

Study Population

Data were retrieved from the nationwide SIBDCS, in which patients with IBD have been prospectively included since 2006

[15]. More than 3,300 patients with CD, ulcerative colitis (UC), and indeterminate colitis (IC), respectively, have been enrolled in the SIBDCS. For the current study and selection criteria, eligible patients have been included and evaluated up to 2016. The cohort study is supported by the Swiss National Science Foundation. The cohort goals and distinct information about methodology are described elsewhere [15]. The manuscript has been written according to the latest STROBE guidelines [16].

Inclusion Criteria

In the first analysis we studied the group of females who were aged ≥ 40 years and diagnosed with IBD before the age of 30 years at time of enrolment in the SIBDCS.

The second analysis refers to longitudinal data on female patients who have attempted to actively conceive and had at least one follow-up after enrolment in the SIBDCS. For this part of the study, we included only females with age < 45 years at time of enrolment in the SIBDCS and who were diagnosed with IBD before the age of 30 years (Fig. 1). Only patients with at least one patient’s questionnaire had to be included due to the fact, that information on children was only provided by patient’s questionnaires.

The third analysis consisted of childless males who actively attempted to conceive.

Results from SIBDCS patients were compared to data on the General Swiss Population (GSP), available from the Swiss statistic centre (Bundesamt für Statistik BfS) [17].

Statistical Analysis

Clinical data were retrieved from the data center of the SIBDCS at the University of Lausanne, (Canton Vaud, Switzerland). The data were available from the cohort based

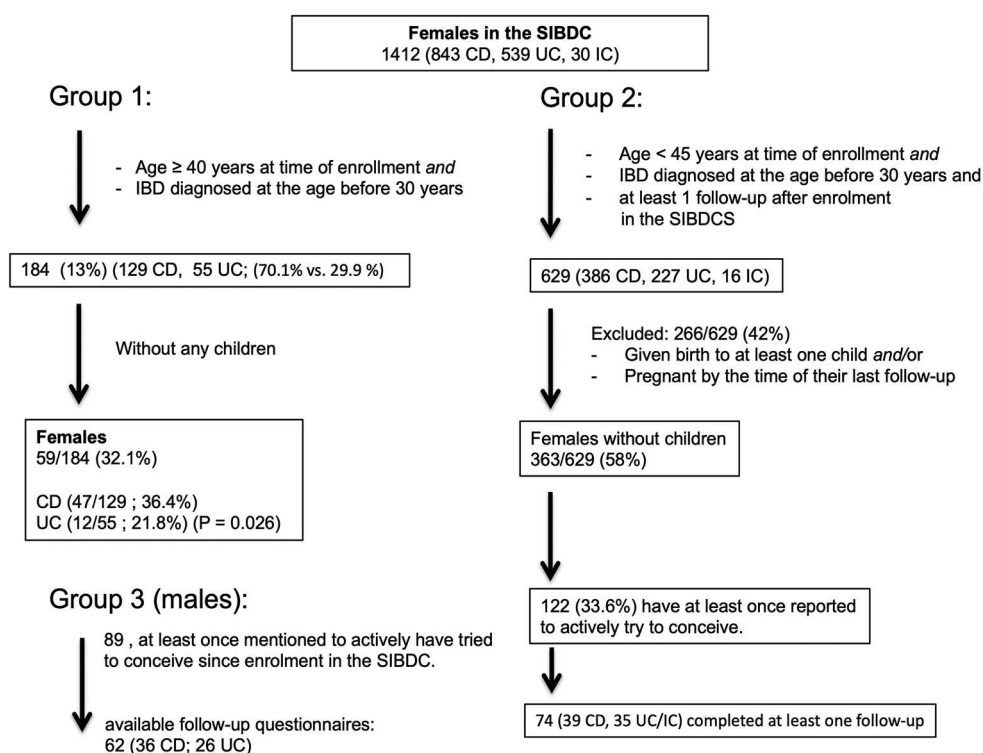


Fig. 1. Flowchart with patient selection algorithm.

on standard questionnaires and annual follow-ups and the enrolment sheet. The Statistical Package for the Social Sciences (version 21; SPSS, Chicago, IL, USA) for PC was used for the statistical analysis. Descriptive statistics were used to depict patients' characteristics. A p-value less than 0.05 (two-tailed) was considered significant.

Ethical Considerations

The Swiss IBD cohort study has been approved by the local Ethical Committees (IRB approval number: EK-1316, approved on 05.02.2007 by the Cantonal Ethics Committee of the Canton Zurich, Switzerland). Written informed consent of each patient was obtained before inclusion in the cohort. The study complied with the last revision of the Declaration of Helsinki principles and with the Guidelines of Good Clinical Practice [18, 19].

RESULTS

Cohort with age \geq 40 years: Comparison of females without vs. with children

A total of 1,412 female patients with IBD were included into the SIBDCS [CD 843 (59.7%), UC/IC 539/30 (40.3%)]. The first analysis included 184 (13%) females in the SIBDCS who aged \geq 40 years were and were firstly diagnosed with IBD before the age of 30 years [CD: 129 (70.1%); UC: 55 (29.9 %)] (Fig. 1 and Table I). Of those, 59 (32.1%) were childless. The portion of childless females of those with CD [47/129 (36.4%)] was significantly higher than the portion of those with UC [12/55 (21.8%)] ($p=0.026$). Overall, 56% of females in the analyzed group were married and 14.1% were single (divorced: 19%, separated 3.3%, widowed 0.5%). The proportion of childless females who were married in this analyzed group was 23.3%. The portion of married females in the childless group was 42.9%, lower than in the group with children (68.7%, $p=0.001$; Table I). The portion of childless females with previous treatment with immunomodulators was higher than the portion of those with children (78% vs. 62.4%, $p=0.036$). Significantly more childless women had history of abscesses than those with children (30.5% vs. 12.8%, $p=0.004$; Table I).

In this group of females (aged \geq 40 years and diagnosed with IBD before the age of 30 years, group 1), the mean number of children per female patient was 1.32 (median 1, min 0, max 6), per female with CD 1.12 (median 1, min 0, max 4), per female with UC/IC 1.78 (median 2, min 0, max 6, $P = 0.001$) (Fig. 2a). The mean number of children per mother was 1.99 (median 2, min 1, max 6), per mother with CD 1.81 (median 2, min 1, max 4), and per mother with UC 2.33 (median 2, min 1, max 6, $P = 0.002$) (Fig. 2b).

Data from the General Swiss Population

Data from the Swiss statistic center [Bundesamt für Statistik (BFS)] [17] revealed that 21.0% of all females with age \geq 40 years in the General Swiss Population (GSP) are childless. The portion of those being married (37.60%; single: 44.33%) is similar to our data from the SIBDCS (42.9%). Among married females in the GSP with age \geq 40 years, 11.6% are childless compared to the higher portion of childless married

female IBD patients in our cohort (23.3%). The proportion of married females with children in the GSP was similar to that of female IBD patients with children in the studied group (72% vs. 68.7%). Overall, 62.6% of females with age \geq 40 years in the GSP are married and 12.1% are single (divorced: 16.0%)

Table I. Demographic and clinical characteristics of female patients with age \geq 40 years, and diagnosed with IBD before the age of 30 years

	Childless (n=59, 32.1%)	With child (n=125, 67.9%)	p
Diagnosis			
CD	47 (79.7)	82 (65.6)	0.052
UC/IC	12 (20.3)	43 (34.4)	
Age at diagnosis [y] (median, IQR; range)	24, 20-27; 9-30	24, 20-28; 9-30	0.935
Age at latest follow-up [y] (median, IQR; range)	45, 43-52; 40-67	46, 43-54; 40-71	0.310
Marital status			
Married	24 (42.9%)	79 (63.2%)	
Single	32 (57.1%)	36 (28.8%)	
Disease duration [y] (median, IQR; range)	23, 17-31; 12-49	25, 19-31; 11-45	0.263
BMI [kg/m ²] (median, IQR; range)	21.8, 19.6-23.7; 16.1-32.3	22.7, 20.4-26.9; 16.2-41.0	0.058
Smoking status at diagnosis			
Non-smoker	26 (44.8)	64 (53.3)	0.287
Smoker	32 (55.2)	56 (46.7)	
Smoking status at enrolment			
Non-smoker	38 (64.4)	86 (71.7)	0.322
Smoker	21 (35.6)	34 (28.3)	
Initial CD location			
L1 (ileal)	6 (12.8)	15 (18.3)	0.395
L2 (colonic)	12 (25.5)	13 (15.9)	
L3 (ileocolonic)	21 (44.7)	44 (53.7)	
L4 (Upper GI only)	0 (0.0)	0 (0.0)	
Unknown/unclear	8 (17.0)	10 (12.2)	
Current CD location			
L1 (ileal)	13 (27.7)	27 (33.3)	0.043
L2 (colonic)	18 (38.3)	17 (21.0)	
L3 (ileocolonic)	10 (21.1)	33 (40.7)	
L4 (Upper GI only)	2 (4.3)	2 (2.5)	
Unknown/unclear	4 (8.5)	2 (2.5)	
Initial UC/IC location			
Pancolitis	5 (41.7)	12 (27.9)	0.251
Left-sided colitis	4 (33.3)	8 (18.6)	
Proctitis	3 (25.0)	14 (32.6)	
Unknown/unclear	0 (0.0)	9 (20.9)	
Current UC/IC location			
Pancolitis	4 (33.3)	16 (36.4)	0.835
Left-sided colitis	5 (41.7)	14 (31.8)	
Proctitis	3 (25.0)	10 (22.7)	
Unknown/unclear	0 (0.0)	4 (9.1)	
Perianal Fistula*	22 (46.8)	26 (31.7)	0.088
Other Fistula*	11 (23.4)	17 (20.7)	0.723
Abscess	18 (30.5)	16 (12.8)	0.004
Stenosis*	26 (55.3)	47 (57.3)	0.826
Intestinal surgery	32 (54.2)	64 (51.2)	0.700
Fistula/abscess surg.*	19 (40.4)	22 (26.8)	0.110
Other surgery	5 (8.5)	17 (13.6)	0.317

Table I (continued)

Therapy (Ever treated)			
5-ASA	44 (74.6)	95 (76.0)	0.834
Antibiotics	30 (50.9)	45 (36.0)	0.056
Steroids	48 (81.4)	100 (80.0)	0.829
Immunomodulators	46 (78.0)	78 (62.4)	0.036
Anti-TNF	22 (37.3)	40 (32.0)	0.479
EIM			
None	25 (42.4)	69 (55.2)	0.104
Yes	34 (57.6)	56 (44.8)	
Formation level			
None or basic	5 (8.8)	26 (21.5)	0.062
Apprenticeship	25 (43.9)	57 (47.1)	
High school	13 (22.8)	14 (11.6)	
Superior	17 (24.6)	24 (19.8)	
SF36 physical component score (median, IQR; range)	45.5, 38.7-53.8 18.5-60.4	46.9, 37.5-54.6 18.5-68.9	0.767
SF36 mental component score (median, IQR; range)	44.0, 32.7-51.3 13.1-57.7	49.6, 33.7-54.8 16.0-60.5	0.186
IBDQoL Scores (median, IQR, range)			
Bowel	53, 42-64, 22-70	56, 47-63, 26-70	0.234
Systemic	21, 17-28, 5-35	23, 18-28, 9-35	0.266
Emotional	60, 52-71, 36-82	66, 54-74, 29-84	0.073
Social	30, 20-34, 8-35	32, 26-35, 7-35	0.036
Anxiety			
No anxiety	38 (64.4)	69 (55.7)	0.673
Mild anxiety	9 (15.3)	27 (21.8)	
Moderate anxiety	9 (15.3)	22 (17.7)	
Severe anxiety	3 (5.1)	6 (4.8)	
Depression			
No depression	45 (76.3)	95 (76.6)	0.507
Mild depression	8 (13.6)	22 (17.7)	
Moderate depression	4 (6.8)	6 (4.8)	
Severe depression	2 (3.4)	1 (0.8)	
Stress			
None to low	19 (33.3)	46 (37.7)	0.917
Low to average	13 (22.8)	27 (22.1)	
Average to high	8 (14.0)	18 (14.8)	
High	17 (29.8)	31 (25.4)	
Type-D Personality			
No	38 (66.7)	91 (74.6)	0.271
Yes	19 (33.3)	31 (25.4)	

Various clinical scores and scales were collected in the SIBDCS to describe patient's personality, quality of life and social environment, in particular the SF-36 score, the Depression Scale, Anxiety Scale, Social environment score, Stress level and the personality type. *CD patients only, 5-ASA: 5-Aminosalicylate acid; BMI: body mass index, CD: Crohn's disease; IBD: inflammatory bowel diseases; IC: indeterminate colitis; IQR: interquartile range; UC: ulcerative colitis; L1-5: location of CD; L1: terminal ileum; L2: colon; L3: ileocolonic; L4: upper gastrointestinal.

(marital status in the studied group of female IBD patients: 56% married, 14.1% single, 19% divorced).

Data from the Swiss statistic center [17] revealed that 20% of females in the age group of 50 to 59 years in the GSP were childless. Based on females' education the frequency of childlessness in this age group varied: 3 of 10 females with high education (university degree) remained childless and 13% of females with low education (only compulsory school education) [17]. In the age group of 30 – 39 years, 24% of females (and 20% of males in this age group) reported VC. In

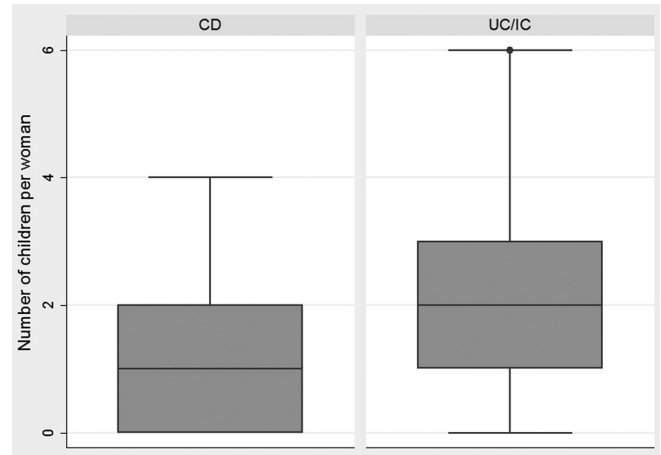


Fig. 2a. Median number of children per woman aged >40 years, diagnosed with inflammatory bowel disease <30 years.

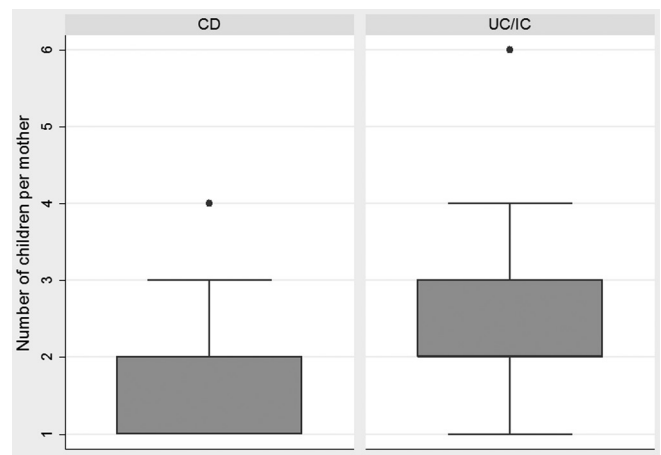


Fig. 2b. Median number of children per mother aged >40 years, diagnosed with inflammatory bowel disease <30 years.

the group of childless females between 20-29 years in the GSP, only 6% reported to wish remaining childless (10% in males), in striking contrast to 86% of childless females (and 67% of childless males) in the age group of 40-49 years.

According to the Swiss statistic center [17] the median number of children per female patient/per mother aged 40 in the GSP was 1.7 per female and 2.2 per mother, respectively. Compared to females of the SIBDCS in this age group, females with UC and females of the GSP have similar numbers of children. Females with CD aged ≥ 40 years of age have significantly less children ($p < 0.001$ for both females and also mothers).

Longitudinal Study

Females Trying to Conceive

Out of those abovementioned 1412 females within the SIBDCS, we analyzed 629 (386 CD, 227 UC, 16 IC) with age < 45 years at time of enrolment in the SIBDCS, who were diagnosed with IBD before the age of 30 years and had filled out at least one patient's questionnaire (Fig. 1). Almost half of females (266/629, 42%) had either born at least one child, or were pregnant to the timepoint of last follow-up. The remaining 363 (58%) females had no children. 122 (33.6%)

had at least once reported to have actively tried to conceive since enrolment. Of those, 74 (39 CD, 35 UC/IC) completed at least one follow-up. Table II encloses demographic and clinical characteristics of those childless females who attempted to conceive, both cumulatively and separately for CD and UC/IC.

Table II. Demographic and clinical characteristics of females aged <45 years, diagnosed with IBD younger than 30 years who reported to have tried to conceive during f/u, separated for females with CD, UC/IC, and also summarized

	CD	UC/IC	Total IBD
Number of patients	39 (52.7)	35 (47.3)	74
Age at diagnosis (median; IQR, range)	21, 18-24 18-39	28, 22-31 17-44	23, 19-30 18-44
Age when trying to conceive (median; IQR, range)	29, 24-34 17-51*	34, 31-39 21-45*	31, 27-36 17-51
% married when trying to conceive	16 (41.0%)	25 (71.4%)	41 (55.4%)
Disease duration when trying to conceive (median; IQR, range)	8, 3-11 0-26	6, 3-9 0-20	6, 3-10 0-26
BMI (median; IQR, range)	20.9, 18.6-22.7 15.6-31.1	21.5, 19.6- 25.2 18.7-34.5	21.0, 19.3- 23.1 15.6-34.5
Medication "Ever treated with", n (%)			
5-ASA	21 (53.8)	34 (97.1)	55 (74.3)
Antibiotics	14 (35.9)	9 (25.7)	23 (31.1)
Steroids	37 (94.9)	27 (77.1)	64 (86.5)
Immunomodulators	34 (87.2)	25 (71.4)	59 (79.7)
Anti-TNF agents	21 (53.8)	12 (34.3)	33 (44.6)
Current therapy when trying to conceive, n (%)			
5-ASA	6 (15.4)	26 (74.3)	32 (32.2)
Antibiotics	1 (2.6)	0 (0.0)	1 (1.4)
Steroids	15 (35.9)	6 (17.1)	20 (27.0)
Immunomodulators	14 (35.9)	15 (42.9)	29 (39.2)
Anti-TNF agents	15 (38.5)	4 (11.4)	19 (25.7)
History of surgery			
Intestinal surgery	9 (23.1)	0 (0.0)	9 (12.2)
Fistula/Abscess surgery	9 (23.1)	1 (2.9)	10 (13.5)
Smoking status			
Non-smoker	26 (66.7)	30 (85.7)	56 (75.7)
Smoker	13 (33.3)	5 (14.3)	18 (24.3)
Formation level			
None or basic	6 (15.4)	3 (8.6)	9 (12.2)
Apprenticeship	20 (51.3)	10 (28.6)	30 (40.5)
High school	3 (7.7)	5 (14.3)	8 (10.8)
Superior	10 (25.6)	17 (48.6)	27 (36.5)
Misscarriages (median, IQR, range)	0, 0-0, 0-3	0, 0-0, 0-2	0, 0-0, 0-3

*Once a 51 year and 45-year-old mentioned "actively trying to conceive". For abbreviations see Table I.

Females with CD were younger at the time of IBD diagnosis (median age 21 years; IQR 18-24 years) than females with UC (median age 28 years, IQR 22-31 years). The median age of females with IBD was 31 years (IQR 27-36 years) when they endeavored to conceive. Out of those, married were 59.2 % (Table III).

Table III. Childless males within the SIBDCS who actively tried to conceive

	CD	UC/IC	Total IBD
Number of patients, n (%)	36 (58.1)	26 (41.9)	62
Age at diagnosis (median; IQR, range)	24; 20-29 4-45	27; 23-34 13-51	25; 21-31 4-51
Age when trying to conceive (median; IQR, range)	27; 30-41 24-54	35; 31-44 21-64	36; 31-42 21-64
Disease duration when trying to conceive (median; IQR, range)	10; 7-16 0-28	7; 4-13 0-25	8; 5-15 0-28
BMI [kg/m ²] (median; IQR, range)	23.7; 23.1- 25.2 18.2-36.2	24.3; 23.1- 25.6 21.7-29.3	24.1; 23.1- 25.5 18.2-36.2
Current therapy when trying to conceive			
5-ASA	5 (13.9)	22 (84.6)	27 (43.6)
Steroids	5 (13.9)	7 (26.9)	12 (19.4)
Antibiotics	1 (2.8)	0 (0.0)	1 (1.6)
Immunomodulators	11 (30.6)	9 (34.6)	20 (32.3)
Anti-TNF Agents	17 (47.2)	4 (15.4)	21 (33.9)
History of surgery			
Intestinal surgery	19 (52.8)	0 (0.0)	19 (30.7)
Fistula/Abscess surgery	11 (30.6)	0 (0.0)	11 (17.7)

For abbreviations see Table I.

Figure 3 (Kaplan-Meier curve) illustrates the cumulative probability of getting pregnant or having a child. Five years after first trying to conceive, 50% of female IBD patients achieved childness or pregnancy.

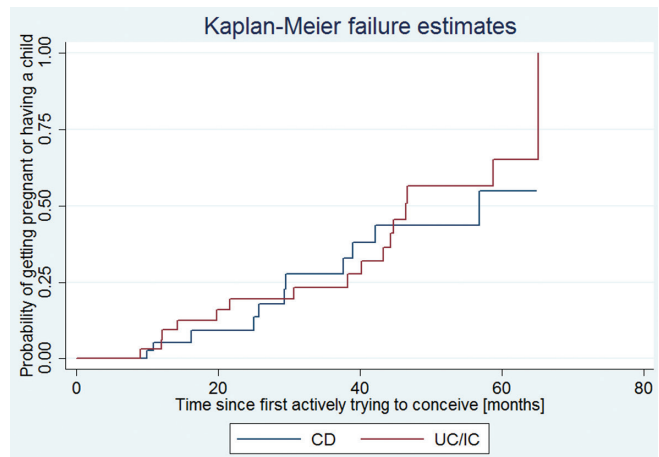


Fig. 3. Cumulative probability of getting pregnant or having a child: Females with Crohn's disease (CD) and ulcerative colitis (UC) or indeterminate colitis (IC).

Males Trying to Conceive

Regarding males, 89 IBD patients claimed at least once having attempted to conceive since enrolment in the SIBDC. Of those, 62 (36 CD; 26 UC) offered available follow-up questionnaires. Demographic and clinical characteristics are enclosed in Table III for all men as well as separated for CD and UC/IC. Their median age at diagnosis was 25 years (IQR 21-31 years), their median age when they tried to conceive 36 years (31-42 years) (Table III).

Fig. 4 depicts the Kaplan Meier diagram regarding the probability of the male IBD patient's partner to get pregnant. After almost 4 years of trying to conceive, 50% of male IBD patients' partners successfully gave birth to a child or were pregnant.

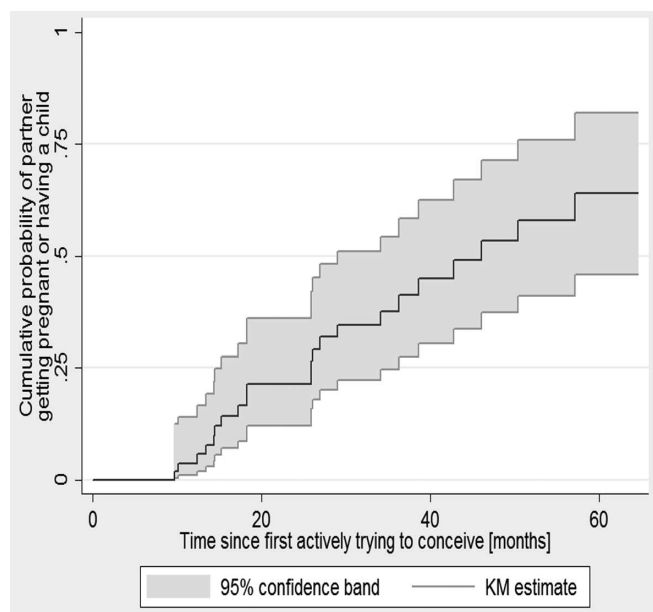


Fig. 4. Cumulative probability of males' partner getting pregnant or having a child.

DISCUSSION

Our analysis from the prospective multi-centre SIBDCS with 1,412 included females provides substantial insights to aspects of childlessness in IBD patients with residency in Switzerland. It reveals that 32.1% of females aged ≥ 40 years and firstly diagnosed with IBD before the age of 30 years are childless. In females with CD, the portion of childless ones was even higher (36.4%), in those with UC, significantly lower (21.8%). In contrast, the rate of females over the age of 40 years without children was 21.0% in the GSP [17].

Childlessness in IBD is a significant topic since there is a lack of relevant data in the literature. Current evidence predominantly addresses pregnancy outcomes in IBD rather than issues of infertility. In a recent German study [4] with similar objective and statistical power of 533 recruited IBD patients, childlessness was reported in 57.4% of the included individuals, 90.6% of whom were women (31% ulcerative colitis and 63% CD). Voluntary childlessness reached 9%. The authors deduced, that poor knowledge was not correlated to elevated VC. Moreover, a previous review published by Tavernier et al. [11] reported the existence of eight studies investigating fertility in CD and seven studies about fertility in UC, published between 1984 and 2009. Most studies included in that review showed a reduction in fertility from 17-44% in females with CD as compared to controls [11]. The rate of fertility was expressed as number of children/women or percentage of pregnant women in the population. Involuntary infertility in females with CD ranged from 5 to 42%, without significant difference to control populations (range 2.5-28%)

[11]. A Scottish population-based study published in 1997 and a referral centre-based US study published in 2007 revealed a raised rate of VC in females with CD (18 and 36%), compared to controls (6.2 and 7%) [5, 12].

Regarding UC, data from the review provided no evidence of decreased fertility in females, compared to controls. For UC patients with surgery, previous meta-analyses have reported rates of infertility of 26-63% following ileal pouch-anal anastomosis for UC in women [20, 21]. However, when using a total laparoscopic approach, similar pregnancy rates were reported in patients having ileal pouch-anal anastomosis for UC or familial adenomatous polyposis (67%) and control patients (71%) who had undergone laparoscopic appendectomy [22]. Furthermore, a very recent meta-analysis (2023) investigated the role of IBD in ovarian reserve functions [23]. The authors included seven original studies and drew the conclusion that female IBD patients can have decreased ovarian reserve function.

Nevertheless, interpretation of fertility data in IBD is difficult and limited by its vast heterogeneity; several studies were population-based, whereas some were case-control and observational ones. Notably, different outcome measures were used to reflect 'fertility'. In our study we intended to evaluate the rate of 'childlessness' as it is known from the literature to be difficult to compare and interpret data from 'infertility studies' due to the fact that a variety of terms and definitions of "infertility" are used, e.g., "infertility", "infecundability", and "childlessness" [24]. "Childlessness" is a simple and objective parameter. However, it implicates both voluntary and involuntary childlessness.

It is substantial to stress that IBD patients remain more frequently VC than non-IBD controls. Several studies revealed that VC is elevated in IBD, based on a variety of reasons, including fear of disease exacerbation, of IBD inheritance, of inability to care for the child, of further stress a child would bring, or of drug interactions – adverse effects during gestation, including teratogenicity [12, 13]. Previous evidence supports at least partly some of the fears, since IBD-related complications are more common than age-matched controls, including infants small for gestational age, spontaneous abortion, preterm birth, and labor as well as delivery complications, all of which are correlated with activity of underlying IBD [8]. In this analysis we were unable to report on the question why females in our cohort who were older than 40 years were childless as the respective information is not available in cohort data base. However, we could assume from general fertility data that the vast majority of women (Switzerland: 96.3%; Germany: 97.5%) get pregnant for the first time before the age of 40 years [25]. In Switzerland, 51.7% of women are aged in their 30s, 43.2% in their 20s, and 1.5% under 20 years old, when they get their first child [25]. The mean age of women in Switzerland at the time of their first life birth is 30.4 years [25]. Therefore, we could derive that childless females aged ≥ 40 years in our cohort were females who were either voluntarily or involuntarily childless or – in other words – would already have had children if they were able to bear a child or really wanted to have children.

Indeed, it is interesting that females with CD exhibited a significantly higher rate of childlessness than females with UC in the group of those aged ≥ 40 years in our cohort. This

finding is also affirmed by the lower mean number of children per woman with CD (1.12), compared to those with UC (1.78), and by the lower mean number of children per mother with CD (1.81), compared to those with UC (2.33). We might speculate that females with CD show a higher rate of VC than females with UC or healthy females in the normal population as we know from another study that involuntary infertility in females did not differ significantly from control populations [11]. However, in the longitudinal analysis we found that it takes a significant amount of time to get pregnant in females with IBD, with similar findings for CD and UC. As shown by a German group, most couples in the general population conceive within six cycles with timed intercourse [26].

Emerging VC in IBD patients indicates that reproductive issues such as fertility and adverse pregnancy outcomes are of substantial concern for many IBD patients, especially women. Selinger et al. [27] demonstrated in 2013, that women in Australia who received appropriate education may alleviate infertility fears and that VC arising from arbitrary and unjustified fears and misconceptions could be lessened. The authors concluded three years later after investigating a UK cohort of IBD female patients, that VC has a multifactorial causality, nevertheless many women remain childless due to poor relevant education-knowledge [28]. Comparable results were reported by a further recent study conducted in Canada and Australia [29]. The authors developed the so-called "Pregnancy in IBD Decision Aid" tool, which offers for gestation an online decision support of IBD females. It was deduced, that IBD individuals who used the aforementioned tool, were characterized by an ameliorated quality of reproductive decision-making as well as IBD-in-pregnancy knowledge. On the contrary, a recent multicenter European study concerning IBD and fertility [7], drew the conclusion that such patients had poor knowledge to what extent IBD may impact fertility and pregnancy. Particularly, 63% of IBD patients claimed not being informed by their healthcare professional and physicians for this substantial issue. A similar negative conclusion was reported by a German study, namely that gastroenterology team members rather rarely refer IBD female patients for fertility therapy consultation, jeopardizing them to remain childless [30].

This knowledge, therefore, should encourage healthcare professionals and physicians involved in the care of IBD patients in the child-bearing age to rely also on appropriate information and envision that IBD nowadays represents a well manageable chronic condition during reproductive age and pregnancy.

Infertility in men with IBD has been even less extensively studied than in their female counterparts [14]. Only very few investigations have addressed male fertility. In the mentioned review published by Tavenier et al. [11] three studies regarding males with CD were included, published between 1986 and 1997. All studies revealed a drop in fertility, compared to controls (1.5-1.75 versus 1.9-2.14). In UC, there was no reduction compared to controls (1.77-2.7 versus 1.9-2.14). Our data could not add specific new insights in the field of male infertility due to lack of appropriate data in the cohort data base. However, we deduced that after almost four years of trying to conceive, only 50% of male IBD patients' partners

successfully achieved their desired target of having a child/being pregnant.

Moreover, a substantial topic regarding VC and IBD patients is undoubtedly the psychological status, which may impact on the outcome of conceive. Indeed, psychosocial factors are known to be more relevant predictors for quality of life than disease activity in IBD patients [31]. In this respect, anxiety is an acknowledged factor that is found more prevalent in IBD women and may impact their decisions and outcome of possible pregnancy [27]. Additionally, a further known "vicious circle" in couples with IBD trying to conceive has been reported with regards to stress: Infertility imposes a negative influence on the psychological health – stress of the couples endeavoring to conceive and vice versa there exists elevated stress which impacts relevantly the ability to conceive [32]. Besides, we have reported previously, that D personality was associated in patients with IBD with depressive symptoms as well as clinical activity [33]. Of note, D personality is also associated with depression and infertility in women [34]. In the same context, IBD patients are characterized by impaired quality of life, which also impact sexual health and fertility [31].

Several limitations of our study necessitate to be addressed. Importantly, we cannot derive information on the specific reasons underlying childlessness in the analysed group, as the cohort questionnaires do not contain specific questions going deeper into detail. Furthermore, we compared two datasets with different methodology of data acquisition (cohort data of the SIBDC and data from the Swiss statistic centre regarding the GSP. More specific data concerning childless or "infertile" females in the GSP are lacking. However, it was the most convenient way to compare IBD patients with non-IBD controls in the general population. Additionally, we were unable to document for all included patients an endoscopic/histologic/clinical remission or relapse at the time of conceive, so a report of this valuable information was not possible.

CONCLUSIONS

Nearly one third of females in the Swiss IBD cohort older than 40 years and diagnosed with IBD before the age of 30 years do not have children. The rate of childlessness in CD is significantly elevated to both, women with UC and from the GSP. Furthermore, the mean number of children is lower in CD than in UC. Although the exact underlying reasons are unknown, this discrepancy should alert health professionals treating CD patients to actively address this topic.

Conflicts of interest: G.R. has consulted to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller; he has received speaker's honoraria from Astra Zeneca, Abbvie, FALK, Janssen, MSD, Pfizer, Phadia, Takeda, Tillots, UCB, Vifor and Zeller; he has received educational grants and research grants from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB and Zeller. L.B. has consulted to Abbvie, Janssen, MSD, Pfizer, Takeda and Vifor; he has received speaker's honoraria

from Astra Zeneca, Abbvie, FALK, MSD, Takeda, and Vifor; he has received educational grants and research grants from Abbvie, MSD and Takeda. The rest of the authors declare no conflict of interest.

Members of the SIBDCS study group: Karim Abdelrahman, Gentiana Ademi, Patrick Aepli, Amman Thomas, Claudia Anderegg, Anca-Teodora Antonino, Eva Archanioti, Eviano Arrigoni, Diana Bakker de Jong, Bruno Balsiger, Polat Bastürk, Peter Bauerfeind, Andrea Becocci, Dominique Belli, José M. Bengoa, Luc Biedermann, Janek Binek, Mirjam Blattmann, Stephan Boehm, Tujana Boldanova, Jan Borovicka, Christian P. Braegger, Stephan Brand, Lukas Brügger, Simon Brunner, Patrick Bühr, Bernard Burnand, Sabine Burk, Emanuel Burri, Sophie Buyse, Dahlia-Thao Cao, Ove Carstens, Dominique H. Criblez, Sophie Cunningham, Fabrizia D'Angelo, Philippe de Saussure, Lukas Degen, Joakim Delarive, Christopher Doerig, Barbara Dora, Susan Drerup, Mara Egger, Ali El-Wafa, Matthias Engelmann, Jessica Ezri, Christian Felley, Markus Fliegner, Nicolas Fournier, Montserrat Fraga, Yannick Franc, Pascal Frei, Remus Frei, Michael Fried, Florian Froehlich, Raoul Ivano Furlano, Luca Garzoni, Martin Geyer, Laurent Girard, Marc Girardin, Delphine Golay, Ignaz Good, Ulrike Graf Bigler, Beat Gysi, Johannes Haarer, Marcel Halama, Janine Haldemann, Pius Heer, Benjamin Heimgartner, Beat Helbling, Peter Hengstler, Denise Herzog, Cyrill Hess, Roxane Hessler, Klaas Heyland, Thomas Hinterleitner, Claudia Hirschi, Petr Hruz, Pascal Juillerat, Carolina Khalid-de Bakker, Stephan Kayser, Céline Keller, (Christina Knellwolf (-Grieger)), Christoph Knoblauch, Henrik Köhler, Rebekka Koller, Claudia Krieger(-Grübel), Patrizia Künzler, Rachel Kusche, Frank Serge Lehmann, Andrew Macpherson, Michel H. Maillard, Michael Manz, Astrid Marot, Rémy Meier, Christa Meyenberger, Pamela Meyer, Pierre Michetti, Benjamin Misselwitz, Patrick Mosler, Christian Mottet, Christoph Müller, Beat Müllhaupt, Leilla Musso, Michaela Neagu, Cristina Nichita, Jan Niess, Andreas Nydegger, Nicole Obialo, Diana Ollo, Cassandra Oropesa, Ulrich Peter, Daniel Peternac, Laetitia Marie Petit, Valérie Pittet, Daniel Pohl, Marc Porzner, Claudia Preissler, Nadia Raschle, Ronald Rentsch, Alexandre Restellini, Sophie Restellini, Jean-Pierre Richterich, Frederic Ris, Branislav Risti, Marc Alain Ritz, Gerhard Rogler, Nina Röhrich, Jean-Benoît Rossel, Vanessa Rueger, Monica Rusticeanu, Markus Sagmeister, Gaby Saner, Bernhard Sauter, Mikael Sawatzki, Michael Scharl, Martin Schelling, Susanne Schibli, Hugo Schlauri, Dominique Schluckebier, Daniela Schmid, Sybille Schmid (-Uebelhart), Jean-François Schnegg, Alain Schoepfer, Vivianne Seematter, Frank Seibold, Mariam Seirafi, Gian-Marco Semadeni, Arne Senning, Christiane Sokollik, Joachim Sommer, Johannes Spalinger, Holger Spangenberger, Philippe Stadler, Peter Staub, Dominic Staudenmann, Volker Stenz, Michael Steuerwald, Alex Straumann, Bruno Strebel, Andreas Stulz, Michael Sulz, Aurora Tatu, Michela Tempia-Caliera, Joël Thorens, Kaspar Truninger, Radu Tutuian, Patrick Urfer, Stephan Vavricka, Francesco Viani, Jürg Vögtlin, Roland Von Känel, Dominique Vouillamoz, Rachel Vulliamy, Paul Wiesel, Reiner Wiest, Stefanie Wöhrle, Samuel Zamora, Silvan Zander, Tina Wylie, Jonas Zeitz, Dorothee Zimmermann.

Authors' contributions: G.R. conceived the idea of the project. M.C.S and M.D. wrote the draft of the manuscript. N. F. and L.B. were responsible for methodology and statistics. J.Z, B. M. and B. I. were involved in the data interpretation. All the authors read and revised

critically the initial draft for intellectual content and approved the final version of the manuscript.

Acknowledgments: This cohort study (SIBDCS) is supported by the Swiss National Science Foundation.

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