



Original Article

Impaired Fertility in Women With Inflammatory Bowel Disease: A National Cohort Study From Sweden

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Abstract

Background and Aims: Inflammatory bowel disease [IBD] has been associated with reduced female fertility. We analyse fertility in a national cohort of women with IBD.

Methods: Fertility was assessed in women with IBD aged 15–44 years in 1964–2014, identified from the Swedish National Patient Register and a matched cohort [ratio 1:5]. Patients with indeterminate colitis or inconsistent IBD coding were classified as IBD-unclassified [IBD-U].

Results: The cohorts included 27 331 women with IBD and 131 892 matched individuals. The fertility rate in IBD was 1.52 (standard deviation [SD] 1.22) births per 1000 person-years and 1.62 [SD 1.28] [$p < 0.001$] in matched individuals. Fertility was impaired in all IBD subtypes compared with the matched cohort (hazard ratio Crohn's disease [CD] 0.88, 95% confidence interval [CI] 0.85–0.91; IBD-U 0.86, 95% CI 0.83–0.89; and ulcerative colitis [UC] 0.96, 95% CI 0.93–0.98). Fertility improved during the study period for the IBD cohort except for CD. Parity progression ratio, the proportion of IBD women progressing from one parity to the next compared with the matched cohort, was decreased at all parity levels for CD and IBD-U, but only for multiparous women in UC. Contraceptive usage was higher in IBD, both before and after the diagnosis. Disease severity, bowel resections, and perianal disease in CD affected fertility negatively.

Conclusions: Fertility was impaired mainly in women with CD and IBD-U, and less so in UC. During the study period, fertility improved in women with UC or IBD-U. Some results suggest a role of voluntarily reduced fertility.

Key Words: Fertility; inflammatory bowel disease

1. Introduction

Onset of inflammatory bowel disease before or during childbearing age is common.¹ Previous studies suggest a reduced fertility [ie, the number of children actually born] in women with active Crohn's disease [CD], but normal fertility in women with CD while in remission

and in women with ulcerative colitis [UC].^{2–4} It is not known to what degree this is due to reduced fecundity [ie, the biological reproductive capacity] or psychosocial factors.^{2,5} Very little is known about the possible effect of inflammatory bowel disease unclassified [IBD-U] on fertility.

Several mechanisms may contribute to the reduced fertility in active CD. The transmural inflammation is believed to cause pelvic inflammation, thereby affecting the fallopian tubes and the ovaries. The serum levels of anti-Müllerian hormone [AMH], which serves as an indicator of the ovarian reserve, is also reduced in women with active CD.^{6,7} There are no available data suggesting any adverse effect of medication against IBD on female fertility,³ but surgery for IBD appears to affect fertility negatively.^{3,8} Moreover, fertility treatment is more common in women with IBD,⁹ but assisted reproduction seems to be less efficient.^{10–12} At the same time, voluntary childlessness is more commonly reported among women with IBD than in the general population.^{13–15}

Most previous studies of fertility or fecundity in women with IBD were based on relatively small, selected groups of patients without an appropriate population for comparison. The aim of this study was to analyse factors associated with variations in fertility in a large cohort of unselected women with IBD. We report the results from the largest population-based national cohort study of fertility, including all women of childbearing age diagnosed with IBD compared with a matched cohort from the general female population. The impacts of the IBD diagnosis, bowel resection, intensity of disease activity, and perianal disease on fertility were assessed.

2. Methods

2.1. Data sources

All Swedish residents are assigned a unique personal identification number which is used in all official registers, thereby enabling linkage between them.¹⁶ The Swedish National Patient Register [NPR] contains information on hospital discharge diagnoses and surgical interventions since 1964, reaching full nationwide coverage by 1987. Since 2001, details on all outpatient specialist care also have been included.^{17,18} The Medical Birth Register [MBR] includes data on practically all deliveries in Sweden since 1973.¹⁹ The Swedish Multi-Generation Register [MGR] contains information on children born to all individuals in Sweden since 1932.²⁰ The Prescribed Drug Register [PDR] provides information on all prescriptions since 2005, but not on drugs given in hospital. Information about socioeconomic status [SES] is found in Longitudinal Integrated Database for Health Insurance and Labour Market Studies [LISA] established by Statistics Sweden [SCB] in 1990.

2.2. Study population

From the NPR we identified a cohort of all female patients with ≥ 2 entries of an IBD diagnosis during the study period 1964–2014. ICD codes for UC, CD, and indeterminate colitis [IC] were used [Supplementary File 1, available as Supplementary data at *ECCO-JCC online*].

It is not always straightforward to decide whether patients with IBD have UC or CD. The term IC should be reserved for patients without a definitive diagnosis even after complete histological analysis of a colectomy specimen. The term IBD unclassified [IBD-U] is increasingly being used for patients with their colon still in place where the clinical presentation is atypical or varying over time. From several schemes proposed to categorise these patients from register data, we used a mildly modified variant of the classification promoted by Everhov *et al.*²¹

The final IBD diagnosis was defined as UC or CD in patients who had a consistent IBD discharge diagnosis. Patients with an initial diagnosis of IC, followed by a later diagnosis of UC or CD, were

accepted as having UC or CD, respectively. Patients with a consistent IC diagnosis, as well as patients with any other combination of UC, CD, or IC diagnoses, were defined as having IBD-U as the final diagnosis. Everhov *et al.* found that UC patients having an additional ICD code for mainly CD-related conditions, like perianal disease and small bowel involvement, should also be classified as having IBD-U in order to minimise misclassification and keep the UC and CD cohorts as consistent as possible.

We assessed the demography and the characteristics of the cohorts, as well as the parity at diagnosis, the number of children born during follow-up, and the achieved parity at end of follow-up. We analysed the impact of the intensity of disease activity, bowel resections, and perianal disease on fertility. IBD patients with a severe flare are usually admitted to hospital in order to receive the most potent medical treatment [eg, intravenous steroids or infliximab]. As details of in-hospital medical treatments are unavailable in the registries, we could not use medical treatment as indicator of intensity of disease activity. It has further been shown that patients with IBD often self-medicate with steroids without a present new prescription.²² Due to these limitations, disease severity was estimated using the order of hospital admissions with a diagnostic code for IBD since the first date of diagnosis, as a time-varying covariate. Bowel resections were identified using intervention codes in the NPR [Supplementary File 1, available as Supplementary data at *ECCO-JCC online*]. Perianal disease was identified using diagnosis codes for anal fistula, abscess, or fissure, and the associated intervention codes.

For comparison, Statistics Sweden [SCB] identified a cohort of women [5:1] from the general population matched for age. As the NPR initially did not have complete national coverage, we also matched for place of residence at date of diagnosis in order to avoid ascertainment bias; 92% of the matching sets consisted of one IBD patient and five matched individuals. In the remaining 8%, the number of matched individuals was reduced due to lack of eligible individuals, but each IBD patient had at least one matched individual.

Information about children born to women in the two cohorts was obtained through linkage with the MBR and the MGR. Information on contraceptive use [including oral contraceptives, vaginal or intrauterine hormonal contraceptives, and subcutaneous hormonal implants] was obtained for both cohorts from the PDR, which provides information on all prescriptions since 2005, and the NPR, which contains codes for insertion of intrauterine non-hormonal contraceptives. Information on SES, obtained from LISA, was used to investigate impact of socioeconomic status.

2.3. Statistical analysis

The characteristics were assessed for the cohorts and sub-cohorts, like age at diagnosis, duration of follow-up, parity at baseline, achieved parity at end of follow-up, and proportion of nulliparae at baseline and at the end of follow-up. Fertility of women in the cohorts was compared by Cox regression, with adjustment for covariates. Because of many childbirths we used Andersen-Gill proportional hazards regression models, taking account of the reduced fertility during pregnancy and 1 year postpartum by using each pregnancy as a time-varying covariate, where applicable. The order of hospital admissions was used as a time-varying covariate to reflect disease severity. The impacts of bowel resection and perianal disease were analysed by Cox regression. The results are expressed as the hazard ratio [HR]. The stratification of sets of IBD patients and matched individuals allowed for different baselines but assumed equal hazard ratios across strata. Stratifications for age intervals and IBD subtypes allowed hazard ratios to differ. For both cohorts, the follow-up of

the occurrence of pregnancy resulting in childbirth started when the case was diagnosed with IBD and ended when they turned 45 years or on 31 December 2014, whichever occurred earliest.

Sensitivity analyses were performed to investigate any impact of socioeconomic status [SES] at diagnosis or of contraceptive use. Information on SES and on contraceptive use was available from 1990 and from 2005, respectively. Thus, only sets matched in 1990 and later were used in the analyses adjusted for SES, and only sets matched in 2005 and later were used in analyses adjusted for use of contraceptives. For SES at diagnosis, we used deciles of disposable income and educational level. Pregnancy protection due to contraceptive use was modelled as a time-varying binary variable, assuming coverage until 90 days after prescription [as every prescription is valid for 3 months].

The parity progression ratio, the proportion of IBD women who progress from one parity to the next compared with the matched cohort, was analysed using logistic regression. Contraceptive use after the IBD diagnosis was investigated as a secondary outcome in sets matched after 2005. Andersen-Gill models were used to take repeated purchases into account. The exposure was defined as number of purchases since 2005. Contraceptive use before IBD diagnosis was investigated by a conditional logistic regression, with matching sets as strata. All regression models used IBD as main exposure, modelled as a yes/no binary variable.

Differences in proportions was analysed with the chi square test. A p -value <0.05 was considered significant. All analyses were performed in Stata 15 [Stata Statistical Software: Release 15, StataCorp LLC, College Station, TX]. The study was approved by the Regional Ethical Review Board in Linköping [registration number of ethical approvals including amendments: 2011/419–31, 2014/226–32, 2014/492–32 and 2015/123–32].

3. Results

3.1. Study population

A cohort of 27 331 women with ≥ 2 entries of an IBD diagnosis was identified from the NPR [12 237 with UC, 8672 with CD and 6422

with IBD-U]. The matched cohort [5:1] included 131 892 women [Table 1]. The mean age at IBD diagnosis of the study cohort was 28.1 [SD 9.2] years, and the mean follow-up time was 10.8 [SD 7.6] years. Patients with CD and IBD-U were younger and had lower parity when diagnosed with IBD compared with UC. Patients with CD were younger than other IBD patients at first surgery, and more likely to be exposed to bowel surgery [45.1%], than patients with IBD-U [37.1%] and UC [14.1%].

A total of 15 737 live births occurred to women with IBD, corresponding to a mean achieved parity at end of follow-up of 1.52 [SD 1.22] live births per 1000 person-years, somewhat lower than in the matched cohort (1.62 [SD 1.28], $p < 0.001$). The achieved parity at end of follow-up was higher in UC [mean 1.59, SD 1.21] compared with CD [mean 1.46, SD 1.23] and IBD-U [mean 1.48, SD 1.23].

The proportion of nulliparae at the end of follow-up was higher in the complete IBD cohort compared with the matched cohort [28.1% vs 26.9%, $p < 0.001$]. Corresponding figures for the IBD subtypes reveal a higher risk of nulliparity in CD [30.8% vs 27.7%, $p < 0.001$] and IBD-U [29.7% vs 27.2%, $p < 0.001$], whereas UC patients were less likely to be nulliparous than their matched individuals [25.3% vs 26.2%, $p = 0.038$].

3.2. Fertility in IBD subsets

Compared with the matched cohort, fertility was lower in the CD cohort (HR 0.88, 95% confidence interval [CI] 0.85–0.91) and in the IBD-U cohort [HR 0.86, 95% CI 0.83–0.89] but only marginally reduced among women with UC [HR 0.96, 95% CI 0.93–0.98] [Table 2]. Fertility was impaired at all ages in women with CD. In UC and IBD-U, fertility was reduced in young women, improving with age, and eventually reaching normal levels in UC [Table 2]. Fertility improved for all subtypes of IBD during the long study period, reaching normal levels in the last decade for UC and IBD-U. For women with CD, the HR plateaued at 0.90 from the 1980s onwards.

An increasing order of hospital admissions was associated with a lower chance of giving birth, particularly for UC and IBD-U patients [Table 3]. An increasing number of bowel resections was associated with decreasing fertility in all subtypes of IBD [Table 4]. Perianal

Table 1. Demography and characteristics of the study cohorts and sub-cohorts of inflammatory bowel disease [IBD] patients from the Swedish Patient Register 1964 to 2014 and population-based, matched individuals.

Characteristics	Matched cohort	IBD cohort	IBD sub-cohorts			
			UC	CD	IBD-U	
Patients, n	131892	27331	12237	8672	6422	
Age at diagnosis, years, mean [SD]	28.1 [9.2]	28.1 [9.2]	29.6 [9.1]	27.3 [8.9]	26.3 [9.4]	
Follow-up time, years, mean [SD]	10.8 [7.6]	10.8 [7.6]	9.4 [7.0]	11.4 [7.9]	12.6 [7.9]	
Bowel surgery, n [proportion]		8016 [29.3%]	1726 [14.1%]	3910 [45.1%]	2380 [37.1%]	
Age at first bowel surgery, mean [SD]		31.9 [10.8]	34.9 [11.4]	30.5 [9.9]	32.3 [11.4]	
Age at first child, years, mean [SD]	26.6 [5.1]	26.6 [5.2]	27.0 [5.1]	26.0 [5.2]	26.6 [5.3]	
Parity at baseline, mean [SD]	0.95 [1.19]	0.92 [1.16]	1.05 [1.18]	0.81 [1.13]	0.80 [1.12]	
Achieved parity at end of follow-up, mean [SD]	1.62 [1.28]	1.52 [1.22]	1.59 [1.21]	1.46 [1.23]	1.48 [1.23]	
Nulliparous at baseline, n [proportion]	69502 [527%]	14614 [535%]	5746 [470%]	5088 [587%]	3780 [589%]	
No child during follow-up, n [proportion]	81615 [619%]	17391 [636%]	8100 [662%]	5441 [627%]	3850 [600%]	
Nulliparity at end of follow-up, n [proportion]	35493 [26.9%]	7679 [28.1%]	3102 [25.3%]	2669 [30.8%]	1908 [29.7%]	
Year of inclusion, n [proportion]						
	1964–1973	6846 [5.2%]	1481 [5.4%]	444 [3.6%]	690 [5.7%]	427 [7.2%]
	1974–1983	18305 [13.9%]	3759 [13.8%]	1286 [10.5%]	1763 [14.6%]	974 [16.4%]
	1984–1993	22607 [17.1%]	4688 [17.2%]	1863 [15.2%]	2223 [18.4%]	1083 [18.2%]
	1994–2003	35409 [26.8%]	7337 [26.8%]	3548 [29.0%]	2750 [22.8%]	1724 [28.9%]
	2004–2014	48725 [36.9%]	10066 [36.8%]	5096 [41.6%]	3090 [35.6%]	1880 [29.3%]

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IBD-U, IBD unclassified; SD, standard deviation.

disease was associated with a further reduced fertility among women with CD; HR was 0.75 [95% CI 0.69–0.82] with perianal disease and 0.90 [95% CI 0.87–0.93] without.

3.3. Parity progression ratio

Parity progression ratio, the proportion of women progressing from one parity to the next, did not differ between women with UC and the matched cohort for women with no children or one child at diagnosis, but was reduced in women that already had two children [Table 5 and Figure 1A]. By contrast, the parity progression ratio

was decreased for the other subtypes of IBD. The most dramatic impact was noted in CD patients with one child before diagnosis, who were much less likely to give birth once (odds ratio [OR] 0.71, 95% CI 0.64–0.79 or twice more [OR 0.64, 95% CI 0.53–0.76] [Figure 1B]).

3.4. Use of contraceptives

Women with IBD used contraceptives more often than the matched individuals, both before and after the IBD diagnosis [Table 6]. Following diagnosis, all types of contraceptives remained more

Table 2. Fertility according to subtypes of IBD compared with matched individuals, expressed as hazard ratios in strata of age and time periods, with adjustment for the protecting effect of ongoing pregnancy and first year postpartum.

	UC		CD		IBD-U	
	HR	95% CI	HR	95% CI	HR	95% CI
Overall	0.96	0.93–0.98	0.88	0.85–0.91	0.86	0.83–0.89
Age-specific fertility						
15–19 years	0.74	0.57–0.97	0.90	0.70–1.14	0.65	0.49–0.86
20–24 years	0.89	0.82–0.97	0.85	0.79–0.92	0.84	0.77–0.92
25–29 years	0.97	0.92–1.02	0.92	0.87–0.96	0.85	0.81–0.91
30–34 years	0.96	0.92–1.00	0.89	0.84–0.94	0.83	0.78–0.88
35–39 years	0.97	0.91–1.04	0.80	0.73–0.86	0.99	0.91–1.08
40–44 years	1.08	0.92–1.26	0.85	0.70–1.04	0.89	0.71–1.12
Fertility in time periods						
1964–1973	0.93	0.82–1.05	0.77	0.69–0.86	0.70	0.55–1.03
1974–1983	0.87	0.80–0.93	0.83	0.78–0.89	0.74	0.69–0.80
1984–1993	0.92	0.86–0.97	0.90	0.85–0.95	0.84	0.79–0.90
1994–2003	0.96	0.92–1.01	0.92	0.87–0.98	0.90	0.85–0.96
2004–2014	1.05	1.00–1.11	0.90	0.84–0.96	1.10	1.01–1.19

HR is hazard ratio with 95% confidence interval [95% CI], with adjustment of time at risk for ongoing pregnancy and first year postpartum as a time-varying covariate.

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IBD-U, IBD unclassified.

Table 3. Impact of disease severity on fertility according to IBD subtypes, expressed as hazard ratio for giving birth in relation to the order of hospital admissions during follow-up.

Order of admissions	UC			CD			IBD-U		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
1	0.82	0.77–0.88	<0.001	0.96	0.89–1.05	0.382	0.87	0.79–0.96	0.006
2	0.83	0.76–0.90	<0.001	0.93	0.84–1.02	0.102	0.79	0.71–0.88	<0.001
3	0.78	0.70–0.87	<0.001	0.88	0.78–0.98	0.020	0.83	0.73–0.93	0.002
>3	0.71	0.65–0.78	<0.001	0.83	0.76–0.92	<0.001	0.63	0.57–0.70	<0.001

HR is hazard ratio with 95% confidence interval [95% CI], with adjustment of time at risk for ongoing pregnancy and first year postpartum as a time-varying covariate.

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IBD-U, IBD unclassified.

Table 4. Impact of abdominal surgery on fertility according to IBD subtype expressed as hazard ratio.

Number of abdominal surgeries	UC			CD			IBD-U		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
0	1.00	0.97–1.03	0.909	0.91	0.88–0.95	<0.001	0.95	0.91–0.98	0.006
1–2	0.65	0.59–0.71	<0.001	0.95	0.90–1.00	0.058	0.75	0.70–0.81	<0.001
3–5	0.55	0.39–0.79	0.001	0.69	0.57–0.84	<0.001	0.43	0.34–0.56	<0.001
6–10	0.72	0.27–1.92	0.512	0.17	0.02–1.22	0.078	-	-	-

Hazard ratio [HR] with 95% confidence interval [95% CI] with adjustment for pregnancy and first year postpartum, age, and time period.

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IBD-U, IBD unclassified.

Table 5. Parity progression ratio [the probability of having one or two additional children] according to parity at diagnosis and subtypes of IBD, compared with matched individuals.

Parity at baseline	Parity progression	UC			CD			IBD-U		
		OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Nulliparous	+1	1.04	0.98–1.09	0.177	0.89	0.85–0.94	<0.001	0.87	0.82–0.92	<0.001
	+2	0.98	0.92–1.04	0.452	0.86	0.81–0.91	<0.001	0.78	0.73–0.84	<0.001
Para 1	+1	1.01	0.93–1.09	0.849	0.71	0.64–0.79	<0.001	0.83	0.74–0.94	0.002
	+2	0.82	0.70–0.95	0.010	0.64	0.53–0.76	<0.001	0.79	0.65–0.95	0.015
Para 2 +	+1	0.87	0.79–0.95	0.003	0.76	0.67–0.86	<0.001	0.87	0.76–1.00	0.053
	+2	0.86	0.70–1.05	0.145	0.70	0.54–0.91	0.007	0.85	0.64–1.15	0.294

No child at baseline [nulliparous], one child at baseline [para 1], and two or more children at baseline [para 2 +].

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn’s disease; IBD-U, IBD unclassified, OR, odds ratio; CI, confidence interval.

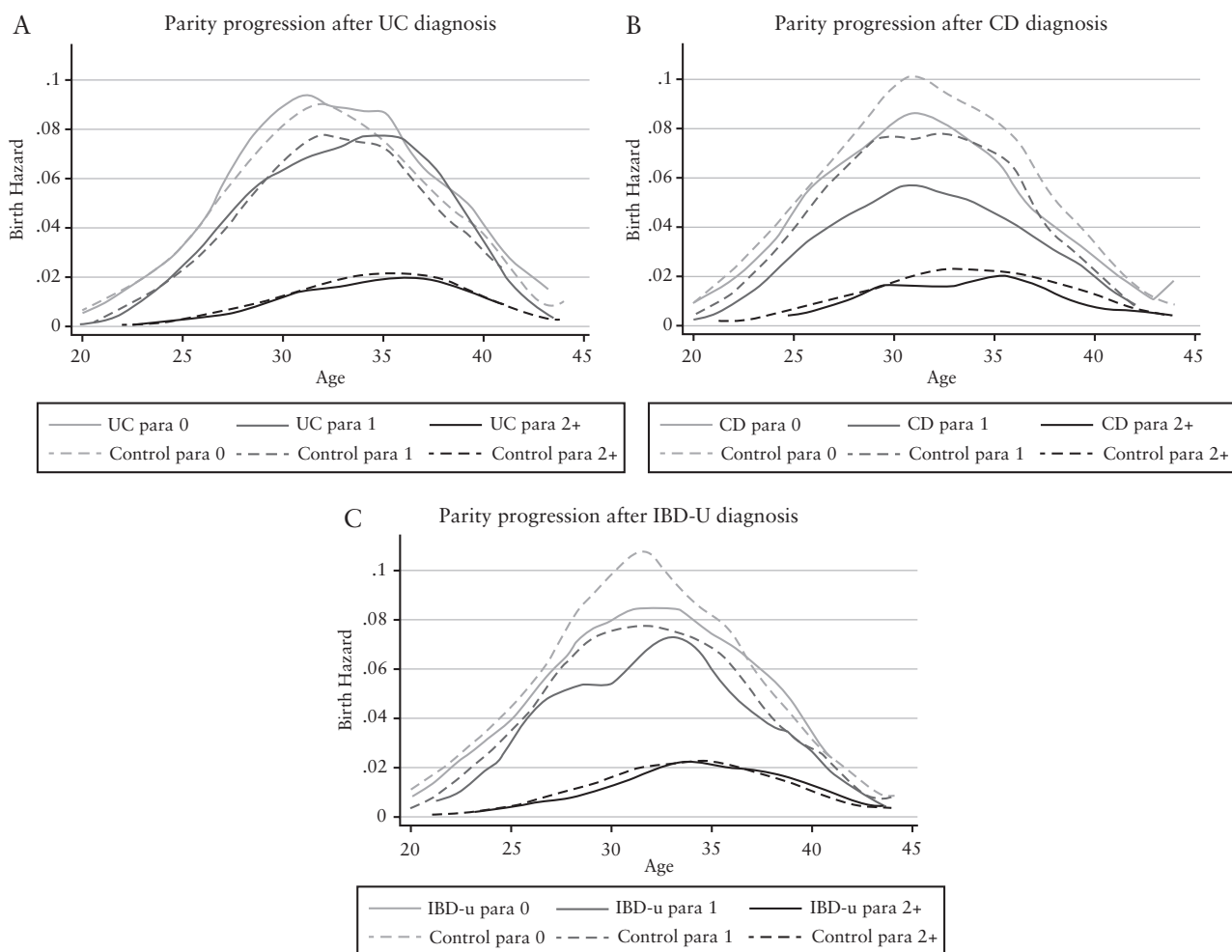


Figure 1. Parity progression illustrated by the intensity in having another child, expressed as the birth hazard, after inflammatory bowel disease diagnosis compared with matched individuals. No child at baseline [para 0], one child at baseline [para 1], and two or more children at baseline [para 2+]. A] Ulcerative colitis. B] Crohn’s disease. C] Inflammatory bowel disease unclassified. Para, parity.

common for all IBD subtypes except for oral contraceptives in UC and IBD-U.

Including socioeconomic status and contraceptive use in multivariable analyses in follow-up data from July 2005 did not change the HR, suggesting there is no difference in impact of these variables between the IBD patients and matched individuals [data not shown].

4. Discussion

This is the largest population-based cohort study of fertility in women with IBD. All women diagnosed with IBD in Sweden between 1964 and 2014 were included. The long average follow-up time and data covering the entire reproductive history of the included women allows for reliable calculations regarding fertility. As a main finding, fertility was reduced in women with CD and IBD-U

Table 6. Use of contraceptives before and after diagnosis according to subtypes of IBD, compared with matched individuals.

Type of contraceptive	Use in relation to date of diagnosis	UC		CD		IBD-U	
		HR	95% CI	HR	95% CI	HR	95% CI
Oral	Before ^a	1.04	1.01–1.08	1.07	1.04–1.11	1.06	1.01–1.11
	After	1.00	0.99–1.02	1.09	1.07–1.12	1.01	0.98–1.04
Vaginal or intra-uterine hormonal	Before ^a	1.11	0.94–1.30	0.97	0.83–1.13	1.17	0.88–1.58
	After	1.67	1.59–1.75	1.99	1.89–2.11	1.90	1.77–2.04
Subcutaneous hormonal implant	Before ^a	1.02	0.75–1.39	1.17	0.80–1.71	1.07	0.64–1.77
	After	1.45	0.53–3.94	2.33	1.01–5.4	2.38	1.09–5.17
Intra-uterine non-hormonal	Before ^a	1.20	0.99–1.46	1.61	1.26–2.05	1.16	0.82–1.65
	After	1.22	0.93–1.61	1.46	1.04–2.07	1.46	0.98–2.18

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IBD-U, IBD unclassified; HR, hazard ratio with 95% confidence interval [95% CI].

^aThe difference in contraceptive use before diagnosis is analysed by logistic regression as odds ratios.

but nearly normal with UC, in accordance with most previous studies of various designs.^{2–4,23–27}

Treatments for IBD have changed profoundly during the long study period, probably affecting the impact of IBD on fecundity. At the same time, fertility patterns have also changed in the wider society over these decades, which may have influenced the desire to have children among women with IBD. However, such changes in fertility patterns and other unknown confounders related to fertility, including body mass index and infertility of the male partner, should be controlled for by the matched cohort study design, as these potential confounders are most likely equally distributed between patients and the matched cohort from the background population.

It is sometimes difficult to classify IBD patients as having either UC or CD. They may present with characteristics that are mixed or may change over time. As a consequence, the registered diagnosis may vary over time. The subgroup of patients who do not consistently meet the diagnostic criteria for UC or CD is variably classified in the literature.^{28,29} The term IBD unclassified [IBD-U] has been proposed for patients lacking characteristic features of UC or CD. The term indeterminate colitis [IC] is commonly used for these patients, but should be reserved to the situation when a definitive diagnosis cannot be reached after colectomy and histopathological examination.³⁰ Of the many alternative classification schemes proposed, we used a conservatively modified variant of the classification recently suggested by Everhov *et al.*²¹ With this approach, we were especially keen to avoid contamination from any misclassified UC and CD patients. The UC and CD cohorts are therefore as clean and robust as can reasonably be achieved. By comparison, the IBD-U cohort is composed of a mixture of IBD subtypes, with a clinical presentation that has been difficult to refer to any of the UC and CD diagnoses. The mixed composition of the IBD-U cohort makes these results difficult to interpret. Worth mentioning though is that in the present study, the fertility in IBD-U is markedly reduced, especially during the most reproductive years. The IBD-U cohort is moreover characterised by the lowest age of onset, the lowest fertility, and the most pronounced impact on fertility by disease severity.

The reduction in fertility was less pronounced in UC and IBD-U during the latter part of the study period, which might be partly explained by the introduction of *in vitro* fertilisation and improved IBD treatment. Another explanation could be the changes in data collection, with inclusion of patients from both in- and outpatient visits from 2001. However, this factor does not appear to have been of any significance in previous studies.³¹ For CD patients, fertility remained impaired throughout.

An increasing disease severity was associated with a decrease in fertility in all subtypes of IBD. This was consistent with the results of the only previous major population-based study of IBD, which used prescription of corticosteroids as surrogate marker for flares.⁴ We judged that hospital admissions would be a more reliable indicator of the intensity of disease activity than prescribed medication, for two reasons. First, patients may start to medicate for symptoms themselves, from previous prescriptions. Second, in-hospital treatments [including some anti-tumour necrosis factors [TNFs]], commonly used to treat flares and even maintenance therapy, are not included in the PDR.

The number of operations, another indicator of disease severity, was associated with reduced fertility. It is not clear whether this is the effect of surgery itself or a consequence of more severe disease. UC patients with no surgery had normal fertility, in accordance with previous studies.^{14,32,33}

A majority of female IBD patients reported decreased sexual activity, in an Australian survey.³⁴ Patients may have decreased libido associated with active disease and experience dyspareunia from active perianal disease, in keeping with our finding that perianal disease in CD had a profound effect on fertility. A decreased ovarian reserve as measured by serum anti-Müllerian hormone has been reported in women with active CD, with a risk of accelerated loss of fertility with age as consequence.^{6,7,35} This is in accordance with our findings, with a more pronounced impact on fertility in women with CD after the age of 30.

Available data do not indicate an adverse effect on fertility from medication against IBD,³ but active disease and flares could impair fertility in other ways, including systemic effects or local inflammation involving reproductive organs, associated depression, malnutrition, and anaemia, which may confound the ability to conceive.^{3,8,36,37} Active disease at the time of conception and during pregnancy may also increase the risk of preterm birth and lower birthweight.³⁸ Women with IBD are therefore recommended to be in remission for 6 months before trying to conceive.^{3,36} Apart from biological reasons, the reduced fertility with more severe disease may therefore be due to physicians' recommendations or reduced sexual desire.

IBD patients had higher contraceptive usage than the matched individuals both before and after diagnosis, in accordance with previous findings.³⁹ Oral contraceptives have been reported to be a risk factor for developing both CD and UC.^{37,40} This association is not necessarily causal as cyclical gastrointestinal symptoms, commonly reported by IBD patients,⁴¹ may be treated with contraceptives.⁴² An increased usage of contraceptives after diagnosis may suggest that voluntary childlessness is more common in IBD.⁴ Choosing to have

fewer children is more common in IBD patients according to survey and interview studies, for reasons including fear of worsening disease during pregnancy, concern for passing IBD on to their offspring, and doubts about the ability to care for a child.¹³

Parity progression ratio is a useful measure in understanding the distribution of cohort fertility,⁴³ but has not previously been applied in IBD. The parity progression ratio is not affected for the first and second child but decreased for higher parity in women with UC, whereas it is markedly decreased at all parity levels in CD and IBD-U. The normal fertility at lower parity but decreased fertility for higher parity in UC may support a voluntary cause to the mildly reduced fertility overall seen in UC.

Although a population-based study has many advantages, there are some limitations. For example, the NPR contains no information on tobacco use. Smoking is known to affect the course of IBD, and smoking may therefore be differentially distributed in the two cohorts. Another limitation with the present study was that the ICD system has been revised four times during the study period. As a result, the same condition may have been coded differently at different times. Most obviously, there was no separate code for IC in ICD9. The National Patient Register reached complete national coverage first in 1987. This should not have an impact on the study results as the comparison cohort was geographically matched, but the earlier results may not be as representative for all of Sweden.

In conclusion, this nationwide cohort study shows impaired fertility in women with CD and IBD-U, and to a lesser extent in UC. Increasing numbers of hospital admissions and bowel resections are associated with reduced fertility in women with all IBD subtypes, as is perianal disease in CD. The increased use of contraceptives and reduced parity progression at higher parities in UC suggest that an element of voluntarily reduced fertility is involved. Encouragingly, the impact of IBD on female fertility, compared with healthy individuals, has become less pronounced during the study period.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

Study concept and design: ED, RA, KL, PM; acquisition of data: RA; analysis and interpretation of data: ED, RA, KL, PM; drafting the manuscript: ED; critical revision of the manuscript for important intellectual content: RA, KL, PM; statistical analysis: UH, RA; obtained funding: ED, KL, RA; study supervision: RA, KL, PM. All authors read and approved the final manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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