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Original Article

Pregnancy and Live Birth Rates Over Time in Women With Inflammatory Bowel Disease: A Population-Based Cohort Study

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Abstract

Background: Inflammatory bowel disease (IBD) negatively affects fertility and fecundity. We aimed to determine longitudinal trends in and factors that affect pregnancy rates in women with ulcerative colitis (UC) and Crohn's disease (CD).

Methods: Women in the University of Manitoba IBD Epidemiology Database aged 15 to 45 were identified between 1992 and 2018 and matched up to 10 non-IBD controls. Pregnancy and live birth rates were compared between women with and without UC or CD stratified by time-period, disease duration and maternal age at conception. Incidence rate ratios (IRR) with 95% confidence intervals (CI) were calculated. Poisson regression was used to adjust these rates for year of pregnancy, disease duration, maternal age, severity of IBD, and prior IBD-related surgery.

Results: Compared to controls, women with UC had lower rates of pregnancies (IRR 0.91, 95% CI: 0.82–0.99) and women with CD had lower rates of pregnancies (IRR 0.85, 95% CI: 0.79–0.93) and live births (IRR 0.83, 95% CI: 0.75–0.92). Although rates of pregnancies and live births were significantly lower in women with UC and CD compared to controls prior to 2010, there appeared to be no differences between the two groups after 2010. Prior intestinal surgery and active disease at conception appeared to lower pregnancy rates in women with UC and CD, respectively.

Conclusion: This study demonstrates that women with IBD have lower pregnancy rates compared to those without IBD, though these differences are no longer evident after 2010. Factors that continue to reduce these rates include prior colectomy and underlying disease activity.

Keywords: *Colitis; Crohn's; Fertility, Fecundity; Pregnancy*

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory condition of the bowel with two distinct phenotypes, ulcerative colitis (UC) and Crohn's disease (CD). It affects both sexes at roughly equivalent rates and is frequently diagnosed in adolescence and early adulthood (1,2). Furthermore, over half of all women with IBD are diagnosed under the age of 30 and up to a quarter of all women with IBD will experience pregnancy after the diagnosis (1,2). Historically, studies have demonstrated that women with IBD experience significant anxiety and fear during pregnancy over concerns including the impact of IBD therapy and inheritability to their unborn child (3–5). In fact, up to 18% of women with CD and 14% of patients with UC experience a reduction in fecundity, the probability of achieving a successful conception, compared to the general population (6,7). Additionally, up to 30% and 16% of women with IBD are at risk of infertility, due to either active disease or prior IBD-related surgery, respectively (8–13). Over time, this translates into an overall reduction in number of pregnancies in women with IBD compared to the general population (11–13).

In recent years, however, guidelines and international societies have emphasized the importance of preconception counselling and overall pregnancy care in IBD (1,2). Whether this increased awareness has translated into an increase in pregnancy rates in women with IBD has not yet been determined. Furthermore, the effect of IBD characteristics, such as disease duration, severity, and surgical history, on pregnancy and live birth rates in women with IBD also remains unknown.

As such, the aim of this study is to evaluate longitudinal trends in pregnancy and live birth rates among women with IBD compared to matched controls in a population-based sample. Furthermore, we aimed to determine which demographic and disease-related factors impact pregnancy rates in women with IBD.

METHODS

This was a retrospective population-based cohort study using the University of Manitoba IBD Epidemiology Database (UMIBDED). Manitoba is a Canadian province with a relatively stable population (1.37 million in 2018) and all residents are registered in Manitoba Health, the provincial universal health-care insurance provider (excepting Canadian armed forces, national police and inmates of federal penitentiaries). The UMIBDED includes all persons resident in the province of Manitoba who have met an established validated administrative definition for IBD (14). Patients with CD are identified if five or more of the last nine IBD contacts contain a CD diagnosis code or more than half of all IBD contacts contain CD diagnosis codes. The same approach is used for a final diagnosis of UC (see Table, Supplementary Data Content 1 for diagnostic codes for UC and CD). This definition has been shown to discriminate patients with CD from those with UC with about 90% accuracy (14). All cases are matched with up to 10 unaffected controls (i.e., no diagnosis of IBD) by age, sex, and geographical area of residence, defined as the first three characters of the postal code. The start of follow-up for controls is indexed to the date of diagnosis for their associated case.

Using a unique provincial health identification number (PHIN), the UMIBDED tracks all outpatient physician visits and inpatient hospitalization events. However, symptom burden, quality of life and endoscopic or histologic data are not included in this database. International Classification of Diseases, 9th revision (ICD-9) codes are used to identify IBD patients prior to 2004 after which ICD-10-CM codes are used.

Study Population

For this study, we focused on women with UC or CD who contributed eligible person-time (EPT) to the UMIBDED between the ages of 15 and 45 at any time between 1992 and 2018. Women with UC or CD contributed person-time from the date of IBD diagnosis or from the day of their 15th birthday if they were diagnosed before age 15. The period of eligible person time ended on day of death, outmigration from Manitoba, up to age 45, having a fertility ending surgical procedure such as a hysterectomy, or the end of follow-up (March 31, 2018). Pregnancies were defined according to a patient having health care visits coded for antenatal diagnoses or procedures, as well as physician tariff codes for antenatal visits or procedures (see Table, Supplementary Data Content 2, which lists antenatal diagnostic codes). The date of delivery was also identified based on diagnosis and procedure codes from the admission records of the mother, as well as physician billing for obstetrical related visits and procedures. These codes were also used to identify stillbirths, abortions, vaginal deliveries, Caesarean deliveries, or multiple gestation (see Table, Supplementary Data Content 2, which lists all pregnancy-related codes). Patients were excluded if they had a fertility ending procedure prior to the IBD diagnosis index date or had a pregnancy event occurring prior to 15 years of age (see Table, Supplementary Data Content 3, which lists diagnostic codes of fertility ending procedures).

Outcomes and Definitions

The primary outcome was to compare pregnancy and live birth rates between persons affected with and without UC or CD. A priori subgroup analysis was planned to determine the impact of year of pregnancy, disease duration and maternal age at conception on pregnancy and live birth rates. In particular, the year of pregnancy was categorized by 1990 to 1999, 2000 to 2009 and 2010 to 2018. Disease duration was divided into less than 1 year, 1 to 4.99 years, and 5 or more years. Finally, maternal age at time of conception was categorized by 15.00 to 24.99, 25.00 to 34.99, and 35.00 to 44.99 years.

Overall pregnancy rates included a composite number of all live births, stillbirths and abortions. Abortions included those that were spontaneous, therapeutic and elective. Live birth rates were defined as those that resulted in a single or multiple birth without a stillborn. The date of UC or CD diagnosis was defined as the first recorded IBD contact. Severe early disease course of UC or CD was defined as an IBD-related hospitalization within 90 days of diagnosis or an IBD-related resective surgery (i.e., ileocecal resection or colectomy) within 90 days of diagnosis or any dispensation of systemic corticosteroids within 180 days of diagnosis; and/or first use of anti-tumor necrosis factor (anti-TNF) or immunomodulator (IMM) within 180 days of diagnosis. Conditional severity at time of conception was defined as any of hospitalization, corticosteroid or biologic dispensation within 180 days prior to the estimated date of conception. Disease remission was defined as lack of these specific features. Finally, an IBD-related surgery was defined as any resective surgery of ileum, colon or rectum occurring after the diagnosis date of CD or a total abdominal colectomy and/or proctectomy or ileoanal anastomosis (IPAA) occurring after the diagnosis date of UC (see Table, Supplementary Data Content 4, which lists all diagnosis codes used to identify IBD-related surgeries).

Statistical Analysis and Ethical Considerations

Incidence rates for pregnancies and live births were expressed as events per 1000 person years (PY) of follow-up. Unadjusted incidence rate ratios (IRR) were calculated, with 95% confidence intervals (CI), to compare rates of pregnancies and live births in women with UC or CD and matched controls for all subgroup analyses. All IRR assumed a Poisson distribution of events and were stratified by year of pregnancy, disease duration and maternal age at conception. Furthermore, a Poisson regression was performed to assess whether a diagnosis of UC or CD was associated with a lower rate of overall pregnancies and live births while adjusting for year of pregnancy, disease duration, maternal age at conception, severity at diagnosis, severity at time of conception and history of IBD-related surgery. All statistical analyses were performed using SAS software. The study protocol was approved by the Manitoba Health Information Privacy Committee and the Health Research Ethics Board of the University of Manitoba.

RESULTS

A total of 532 pregnancies occurred in women with UC, of which 394 were live births, over 7,276 person-years of follow-up compared to 2876 pregnancies and 2807 live births in matched controls over 46,188 person years (Table 1). Compared to matched controls, women with UC had lower rates of pregnancies (adjusted RR 0.91, 95% CI: 0.82–0.99) though differences in live birth rates did not reach statistical significance (adjusted RR 0.92, 95% CI: 0.83–1.02). A total of 637 pregnancies occurred in women with CD, of which 447 were live births, in 8479 person-years

of follow-up, and 5094 pregnancies and 3670 live births occurred in matched controls over 56,663 person years. Women with CD had lower rates of pregnancies (adjusted RR 0.85, 95% CI: 0.79–0.93) and live births (adjusted RR 0.83, 95% CI: 0.75–0.92).

Rates of Pregnancies Over Time in Women With UC or CD

Women with UC had lower pregnancy and live birth rates than matched controls between 2000 and 2009 (Figure 1a and b; Table 2). Similarly, women with CD also had lower pregnancy and live birth rates than matched controls during this time-period (Figure 1c and d; Table 2). After 2010, however, rates of pregnancies and live births were not statistically significant between women with either UC and CD and their matched controls (Table 2).

Impact of Disease Duration on Rates of Pregnancies in Women With UC or CD

Compared to matched controls, women with UC had similar incidence rates of pregnancies (Figure 2a) and live births

Table 1. Incidence rate per person years (PY) of pregnancies in women with inflammatory bowel disease matched to healthy controls, stratified by ulcerative colitis and Crohn's disease

	Number (n)	Incidence per 1000 PY	Number (n)	Incidence per 1000 PY	Unadjusted Rate Ratios (95% CI)	Adjusted Rate Ratios (95% CI)
	Ulcerative colitis		Controls			
Overall pregnancies	532	73.1	2876	83.9	0.87 (0.80–0.95)	0.91 (0.82–0.99)
Live births	394	54.2	2807	60.8	0.89 (0.80–0.99)	0.92 (0.83–1.02)
	Crohn's disease		Controls			
Overall pregnancies	637	75.1	5094	89.9	0.84 (0.77–0.91)	0.85 (0.79–0.93)
Live births	447	52.7	3670	64.8	0.81 (0.74–0.89)	0.83 (0.75–0.92)

Poisson regression analysis adjusted for time-period of conception, disease duration, maternal age at conception, severity at diagnosis and conception, and history of IBD surgery.

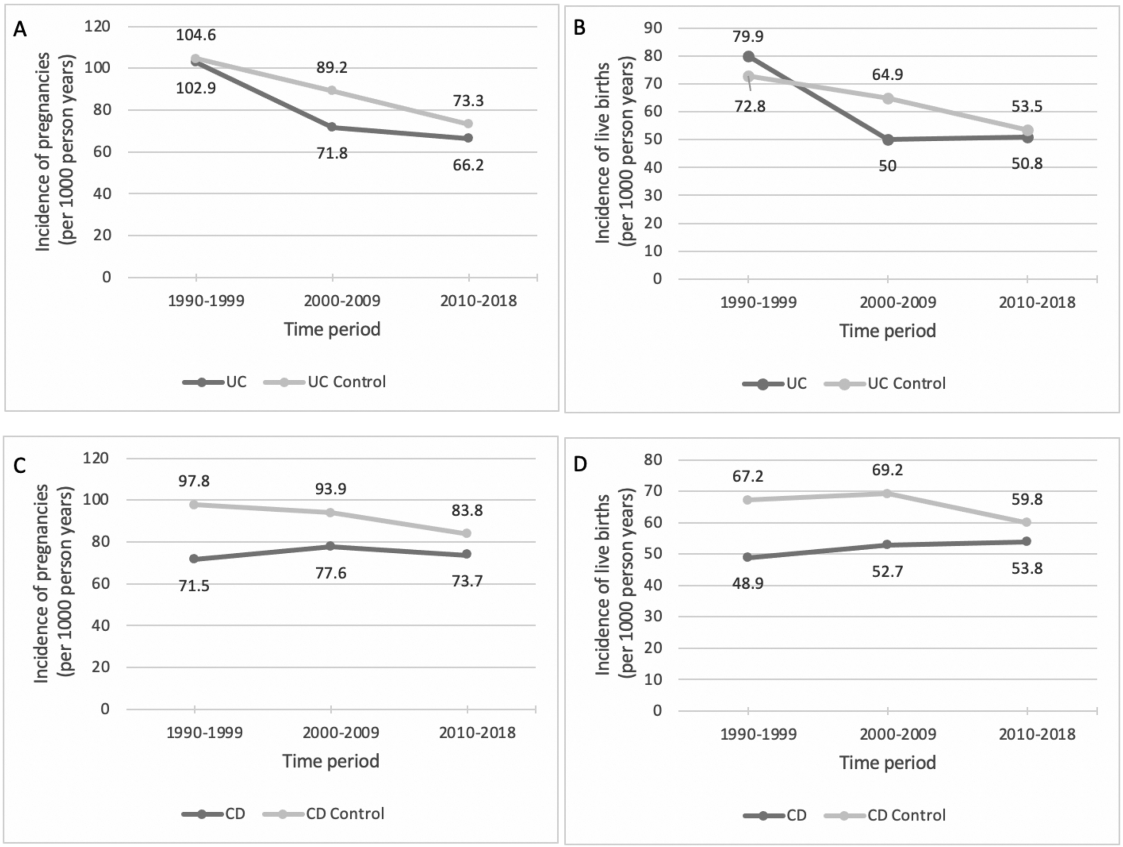

Figure 1. Incidence per 1000 person years of (a) overall pregnancies over time in women with ulcerative colitis; (b) live births over time in women with ulcerative colitis; (c) overall pregnancies over time in women with Crohn's disease; and (d) live births over time in women with Crohn's disease.

(Figure 2b) regardless of disease duration (Table 2). Women with CD had a significant reduction in the incidence of pregnancy (Figure 2c) and live births (Figure 2d) regardless of disease duration (Table 2). In particular, the IRR for pregnancies and live births was 0.47 (95% CI: 0.33–0.67) and 0.35 (95% CI: 0.22–0.57), respectively, for women with CD compared to matched controls in the first year following diagnosis (Table 2).

Impact of Maternal Age on Pregnancy Rates in Women With UC or CD

The incidence rates of pregnancies (Figure 3a) and live births (Figure 3b) remained generally similar for women with UC compared to controls regardless of maternal age at conception other than those with age > 35 (Table 2). In contrast, women with CD had lower rates of pregnancies (Figure 3c)

Table 2. Incidence rate ratios (IRR) for overall pregnancies and live births for women with ulcerative colitis and Crohn's disease, compared with age matched controls, stratified by time-period of pregnancy, disease duration and maternal age at conception

	Ulcerative Colitis		Crohn's disease	
	IRR (95% CI) (Overall pregnancies)	IRR (95% CI) (Live births)	IRR (95% CI) (Overall pregnancies)	IRR (95% CI) (Live births)
Time Period				
1990–1999	0.98 (0.79–1.22)	1.10 (0.86–1.41)	0.73 (0.58–0.93)	0.73 (0.55–0.97)
2000–2009	0.81 (0.70–0.93)	0.77 (0.65–0.91)	0.83 (0.73–0.93)	0.76 (0.66–0.88)
2010–2018	0.90 (0.79–1.04)	0.95 (0.81–1.12)	0.88 (0.78–1.00)	0.90 (0.78–1.04)
Disease duration				
<1.00 year	0.71 (0.53–0.96)	0.73 (0.51–1.03)	0.47 (0.33–0.67)	0.35 (0.22–0.57)
1.00–4.99 years	0.92 (0.79–1.06)	0.95 (0.80–1.12)	0.85 (0.75–0.98)	0.82 (0.70–0.97)
5.00+ years	0.87 (0.77–0.99)	0.89 (0.76–1.03)	0.89 (0.80–0.99)	0.89 (0.78–1.00)
Age at conception				
15.00–24.99	0.73 (0.58–0.92)	0.77 (0.58–1.03)	0.75 (0.61–0.92)	0.74 (0.56–0.97)
25.00–34.99	0.97 (0.87–1.08)	1.01 (0.89–1.14)	0.87 (0.79–0.97)	0.86 (0.76–0.96)
35.00–44.99	0.82 (0.67–1.02)	0.72 (0.55–0.93)	0.88 (0.72–1.07)	0.78 (0.61–1.01)

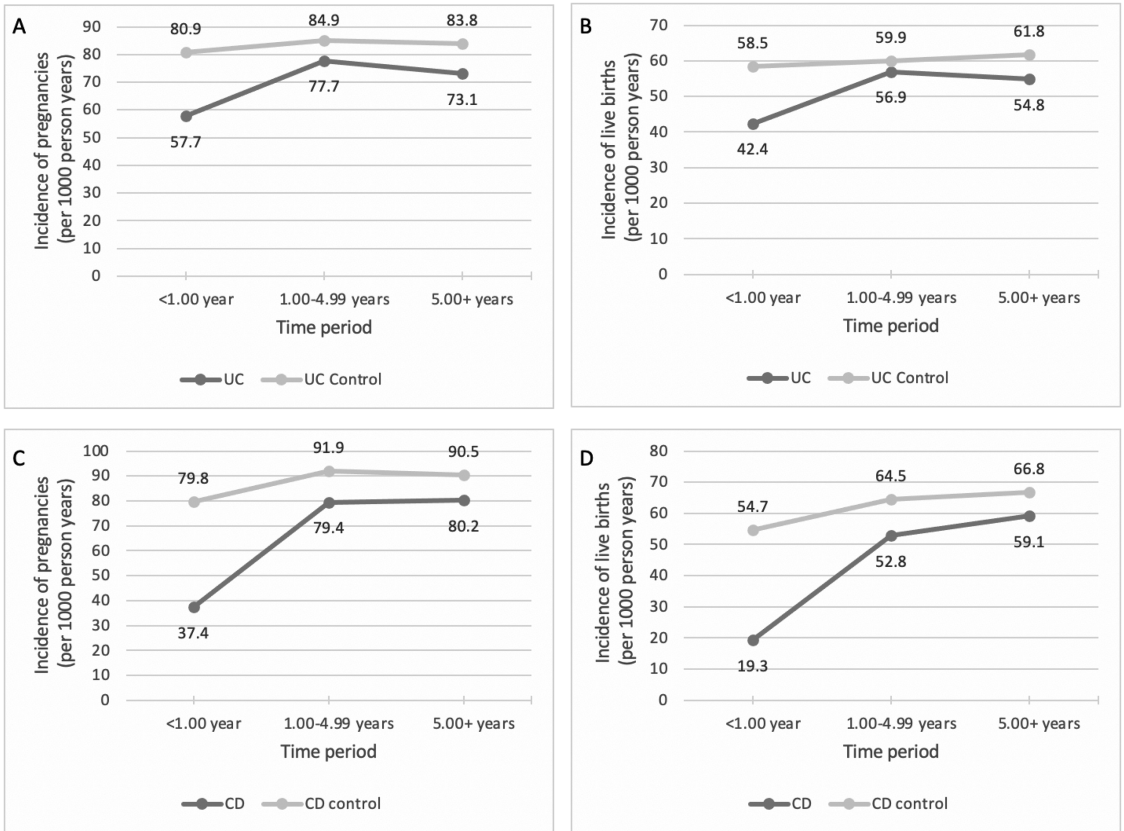

Figure 2. Impact of disease duration on incidence per 1000 person years of (a) overall pregnancies in women with ulcerative colitis; (b) live births in women with ulcerative colitis; (c) overall pregnancies in women with Crohn's disease; and (d) live births in women with Crohn's disease.

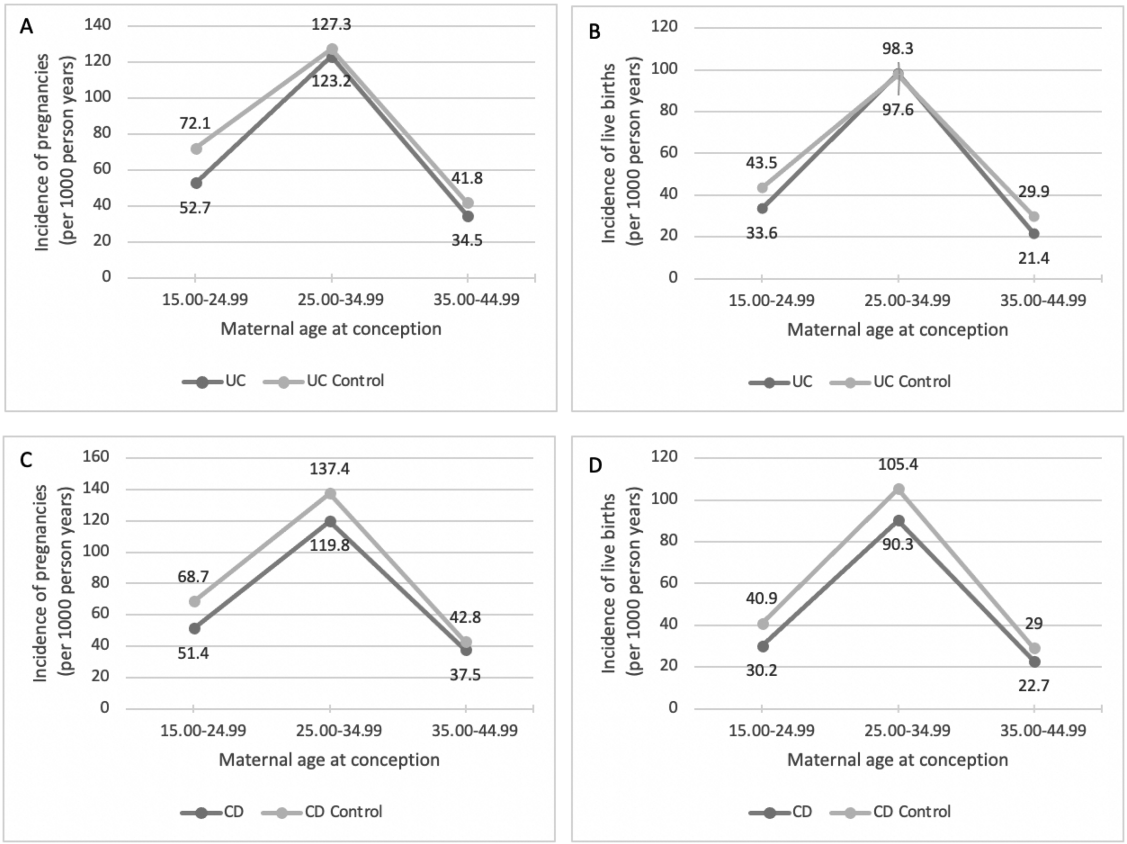

Figure 3. Impact of maternal age at time of conception on incidence per 1000 person years of (a) overall pregnancies in women with ulcerative colitis; (b) live births in women with ulcerative colitis; (c) overall pregnancies in women with Crohn's disease; and (d) live births in women with Crohn's disease.

and live births (Figure 3d) regardless of maternal age of conception (Table 2).

Multivariable Poisson Regression Analysis for Pregnancy Rates

Compared to pregnancies occurring before 1990, women with UC had a decline in pregnancy and live birth rates from 2000 to 2018 (Table 3). Furthermore, compared to disease duration of less than 1 year, both women with UC and CD had significantly higher rates of pregnancies and live births with disease durations greater than 1 year. In fact, women with disease duration for more than 5 years had a significant increase in pregnancy rates compared to those with a disease duration less than 1 year in UC (adjusted IRR 1.59, 95% CI: 1.15–2.20) and in CD (adjusted IRR 2.22, 95% CI: 1.53–3.23).

Compared to those in remission, women with features of severe CD were less likely to have a pregnancy in the next 9 months and have a child 9 months later than women with less severe CD (adjusted IRR 0.68, 95% CI: 0.47–0.99 for pregnancies and 0.57, 95% CI: 0.35–0.93 for live births; Table 3). Finally, persons with UC and a history of IPAA surgery also had significantly lower pregnancy (adjusted IRR 0.66, 95% CI: 0.46–0.94) and live birth (adjusted IRR 0.59, 95% CI: 0.38–0.89) rates compared to those with UC and no history of IPAA.

DISCUSSION

In this study, we demonstrate that rates of pregnancies and live births are lower in women with IBD compared to matched controls. Furthermore, active disease at time of conception, a new diagnosis of IBD and prior IPAA surgery appeared to reduce pregnancy and live birth rates in women with IBD which is consistent with previous studies (7,15).

Reassuringly, we demonstrate that the rates of pregnancies have become comparable to the general population over time, with no significant differences between cases and controls after 2010. Although reasons for this could not be definitively identified using the data available, this improvement in pregnancy rates may reflect the impact of a number of positive factors, including more widely available fertility options such as assisted reproductive therapies (16), improved pregnancy-specific education (16), improved preconception care (16) and increased adherence to IBD-related therapies during pregnancy which in turn improves rates of disease remission (1,2). Similarly, an increase in biologic use during the study time-period may also reflect improved disease control and improved rates of pregnancy (17). Finally, increased frequency of family-planning discussions in ambulatory gastroenterology clinics may improve fecundity by improving IBD-related pregnancy knowledge and clarification of common misconceptions (3), though this remains to be confirmed in future studies.

However, several factors may continue to reduce pregnancy rates in women with IBD, particularly those with CD. Women with CD under age 35 had significantly lower pregnancy rates compared to matched controls, which is in concordance with what has been previously reported (11). Furthermore, disease duration also appeared to significantly

Table 3. Adjusted incidence rate ratios (IRR) calculated by Poisson regression analysis adjusted for time-period of conception, disease duration, maternal age at conception, severity at diagnosis and conception, and history of IBD surgery

	Ulcerative Colitis		Crohn's disease	
	IRR (95% CI) (Overall pregnancies)	IRR (95% CI) (Live births)	IRR (95% CI) (Overall pregnancies)	IRR (95% CI) (Live births)
Time period				
1990–1999	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
2000–2009	0.69 (0.53–0.89)	0.61 (0.45–0.82)	0.94 (0.72–1.23)	0.89 (0.65–1.23)
2010–2018	0.64 (0.49–0.83)	0.63 (0.47–0.85)	0.93 (0.70–1.22)	0.94 (0.67–1.31)
Disease duration				
<1.00 year	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
1.00–4.99 years	1.39 (1.01–1.89)	1.38 (0.96–1.98)	2.03 (1.41–2.93)	2.61 (1.58–4.32)
5.00+ years	1.59 (1.15–2.20)	1.64 (1.12–2.39)	2.22 (1.53–3.23)	3.06 (1.84–5.09)
Age at conception				
15.00–24.99	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
25.00–34.99	2.15 (1.67–2.76)	2.69 (1.98–3.65)	2.10 (1.67–2.63)	2.60 (1.95–3.48)
35.00–44.99	0.58 (0.43–0.80)	0.57 (0.39–0.84)	0.65 (0.49–0.86)	0.64 (0.44–0.92)
Severity at diagnosis				
Yes	0.92 (0.76–1.12)	0.98 (0.78–1.22)	0.91 (0.77–1.07)	0.89 (0.73–1.08)
No	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Severity at conception				
Yes	0.81 (0.54–1.21)	0.90 (0.58–1.40)	0.68 (0.47–0.99)	0.57 (0.35–0.93)
No	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
History of IBD surgery				
Yes	0.66 (0.46–0.94)	0.59 (0.38–0.89)	0.84 (0.68–1.02)	0.83 (0.66–1.05)
No	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)

affect pregnancy rates. In fact, we observed significantly lower incidence rates of pregnancies and live births, respectively, in women with CD with a disease duration less than 1 year compared to matched controls. The first year after an IBD diagnosis is characterized by active, uncontrolled inflammation (1,2), which can lead to a higher risk of hospitalizations (18), disease relapse (19), and uncertainty for patients with respect to understanding their chronic illness and medications required to achieve disease control. This may also coincide with an increased risk of sexual dysfunction and decreased desire for pregnancy due to abdominal pain and dyspareuenia (20). This inevitably shifts the overall focus away from other important aspects of life, some of which are fundamental quality of life measures, such as preconception and family-planning.

In addition, there appeared to be a significant reduction in pregnancy and live birth rates in women with severe CD compared to those without severe CD. A similar phenomenon was not observed in women with UC. Potential reasons for this discrepancy between CD and UC include a greater disease burden, including perianal manifestations, and increased risk of IBD-related hospitalization in women with CD which may in turn decrease fecundity (20,21). Furthermore, the transmural disease process in CD leads to increased risk of intestinal resections and adhesions which may increase the risk of infertility (1,2). Unfortunately, using administrative data we could not be certain as to the impact of these disease-related features on overall pregnancy rates.

Finally, we observed a significant decline in pregnancy and live birth rates in women with UC post IPAA surgery. This may be due to an increased risk of infertility, rather than pregnancy loss, from surgery-related abdominal adhesions and fallopian tube scarring (22,23). Furthermore, we were not able to differentiate between open and laparoscopic IPAA surgery as prior studies have suggested that a laparoscopic approach may reduce the risk of adhesions and improve overall fertility rates in patients with IBD (24).

To the best of our knowledge, this is the first administrative database study to explore pregnancy rates over time in women with IBD and compare them to matched controls. A major strength is the inclusion of large number of women with UC and CD. There remains, however, some inherent limitations. Firstly, pregnancy events were determined based on ICD codes and not confirmed by laboratory or radiologic investigation. As such, early pregnancy loss or elective termination of pregnancy may not have been recorded accurately which may have led to an underestimation of pregnancy rates. It is possible that the high rates of pregnancy loss observed maybe due to first trimester spontaneous miscarriage, similar to the general population. Furthermore, the lack of endoscopy and clinical data in the database prevents a thorough assessment of the impact of disease activity on overall pregnancy rates. Our definition of disease severity may not correlate with the true degree of inflammation, which may in turn limit the analysis on the overall number of pregnancies and live births. Given the study design, we cannot reliably attribute the overall reduction in total and live pregnancies in patients with IBD to either a

reduction in fecundity or infertility. This can realistically only be confirmed in population studies that include only patients actively trying to conceive (i.e., those visiting fertility clinics) or large observational studies. Finally, other factors that may affect the number of pregnancies and live births, such as prior obstetrical or gynecological history, fertility treatments, and pelvic surgery were not assessed for in this study and may result in confounding biases. Similarly, the impact of biologic use, medication adherence, and preconception and pregnancy counselling on the overall rates of pregnancies and live births in women with IBD could not be determined due to lack of available data.

CONCLUSION

We demonstrate that women with UC and CD have lower pregnancy rates compared to those without IBD, though these differences were not apparent after 2010. However, factors that continue to independently reduce pregnancy rates in women with UC and CD include a shorter disease duration, severe disease at time of conception, and prior IPAA surgery. As such, family-planning discussions and preconception care should be incorporated early in the IBD course to allow patients to make informed decisions in their child-bearing years.

Supplementary Data

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

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Conflict of Interest

P.T., A.T., and R.G. have no conflict of interest to declare. V.H. has served as a speaker for Abbvie, Janssen, Ferring and Takeda and has served on advisor committees or review panels for Abbvie, Janssen, Pfizer, Merck, Takeda, Ferring, and Roche. L.T. has received investigator-initiated funding from Janssen Canada; served on advisory boards for AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada, Janssen Canada, Sandoz Canada, Amgen Canada, and Roche Canada; and received infrastructure funding from Abbvie, Takeda, Sandoz, Amgen, Pfizer and Gilead. C.N.B. is supported by the Bingham Chair in Gastroenterology, has served on advisory Boards for AbbVie Canada, Amgen Canada, Avir Pharmaceuticals, Bristol Myers Squibb Canada, Roche Canada, Janssen Canada, Sandoz Canada, Takeda Canada and Pfizer Canada; Consultant for Mylan Pharmaceuticals and Takeda; received educational grants from Abbvie Canada, Pfizer Canada, Takeda Canada, and Janssen Canada; served on the Speaker's panel for Abbvie Canada, Janssen Canada, Medtronic Canada, and Takeda Canada; and received research funding from Abbvie Canada, Pfizer Canada and Sandoz Canada.

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