Surgery for Inflammatory Bowel Disease Has Unclear Impact on Female Fertility: A Cochrane Collaboration Systematic Review

Sangmin Lee, MSc1, Megan Crowe, MSc2, Cynthia H. Seow, MBBS, MSc1,3, Paulo G. Kotze, MD, PhD4, Gilaad G. Kaplan, MD, MPH1,3, Amy Metcalfe, PhD1,3, Amanda Ricciuto, MD, PhD6, Eric I. Benchimol, MD, PhD2,7,8, M. Ellen Kuenzig, PhD7

1Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; 2School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; 3Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; 4IBD Outpatients Clinic, Colorectal Surgery Unit, Catholic University of Paraná (PUCPR), Curitiba, Brazil; 5Department of Obstetrics and Gynecology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; 6Division of Gastroenterology, Hepatology, and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada; 7Children's Hospital of Eastern Ontario (CHEO) Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Eastern Ontario and CHEO Research Institute, Ottawa, Ontario, Canada; 8Department of Pediatrics, University of Ottawa, Ottawa, Ontario, Canada

Benchimol and Kuenzig contributed equally to this work.

Correspondence: M. Ellen Kuenzig, PhD, Children's Hospital of Eastern Ontario Research Institute, 401 Smyth Road, Ottawa, ON, K1H 8L1, Canada, e-mail: mkuenzig@cheo.on.ca

Abstract

Background and Aims: Surgical treatment of inflammatory bowel disease (IBD) may impair female fertility. We conducted a systematic review to determine the risk of infertility and pregnancy outcomes in women with IBD who underwent surgery.

Methods: We identified studies evaluating the impact of IBD surgery on infertility and pregnancy outcomes. Risk ratios (RR) and 95% confidence intervals (CIs) were pooled when data were presented using contingency tables. Odds ratios (OR) were pooled when raw numbers were not provided. GRADE was used to evaluate the certainty of evidence.

Results: Sixteen observational studies were included, comparing women with and without surgery, open and laparoscopic surgery and before and after surgery. All studies were of low quality. The effect of surgery on infertility at 12 months (RR 5.45, 95% CI 0.41 to 72.57) was uncertain. Similarly, the fertility effects of laparoscopic versus open surgery method were unclear (RR 0.70, 95% CI 0.38 to 1.27). The impact of IBD surgery on pregnancy outcomes should be interpreted with caution. Surgery was associated with miscarriage (OR 2.03, 95% CI 1.14 to 3.60), use of assisted reproductive technologies (RR 25.09, 95% CI 1.56 to 403.76) and caesarean section (RR 2.23, 95% CI 1.00 to 4.95), but not with stillbirth (RR 1.96, 95% CI 0.42 to 9.18), preterm birth (RR 1.91, 95% CI 0.67 to 5.48), low birth weight (RR 0.61, 95% CI 0.08 to 4.83) or small for gestational age (RR 2.54, 95% CI 0.80 to 8.01).

Conclusion: The effect of surgical therapy for IBD on rates of female infertility and pregnancy-related outcomes was uncertain due to poor quality of existing literature.

Keywords: Crohn’s disease; Fertility; Infertility; Inflammatory bowel disease; Surgery; Ulcerative colitis
Background
Within 10 years, 50% of Crohn’s disease (CD) and 15% of ulcerative colitis (UC) patients require surgery due to medically refractory or complicated disease (1). Ileal pouch-anal anastomosis (IPAA) following colectomy is common in UC patients. Between 44% and 82% of women are infertile following IPAA; in comparison, 0 to 38% of women without IPAA are infertile (2,3). The effect of other surgical procedures remains unknown.

Our review evaluated the effects of surgical interventions on female infertility and their impact on the need for assisted reproductive technology (ART), time to pregnancy and pregnancy outcomes. This report is based on a systematic review and meta-analysis conducted for the Cochrane Collaboration (4).

METHODS
This systematic review was conducted based on a previously published protocol (5) and reported in accordance with the PRISMA guidelines (6).

Study Identification and Selection
Interventional or observational studies of women of reproductive age (≥12 years) with inflammatory bowel disease (IBD) published in any language were included. Eligible studies compared infertility and/or secondary outcomes between IBD patients with and without surgery or with different surgical techniques (e.g., open versus laparoscopic). Studies comparing IBD to non-IBD controls or combining IBD patients with those undergoing similar surgeries for non-IBD indications were excluded. Cross-over studies, case series and case reports were excluded.

MEDLINE, EMBASE, Cochrane CENTRAL and the Cochrane IBD Group Specialized Register were searched for eligible studies from inception to September 27, 2018 (Supplementary Appendix). Additional studies were identified from references of relevant articles, conference abstracts, trials registers and grey literature databases.

Two authors (S.L. and M.C.) independently screened abstracts for eligibility and independently reviewed full texts for inclusion. Disagreements were resolved by consensus with C.H.S., E.I.B. or M.E.K.

Comparisons
We compared infertility and secondary outcomes in women with and without any previous IBD surgery (intra-abdominal or perianal) and with open and laparoscopic surgery (IPAA only). We also describe outcomes in women before and after surgery.

Outcomes
Our primary outcome was infertility defined as an inability to become pregnant after 1 year of regular unprotected sexual intercourse without birth control. Secondary outcomes included infertility at 6, 18 and 24 months, miscarriage, stillbirth, use of ART (hormonal or mechanical treatments and in vitro fertilization), mode of delivery, prematurity (delivery before 37 weeks of gestation), low (<2500 g) or very low (<1500 g) birth weight, small for gestational age (<10th percentile), gestational diabetes, preeclampsia and time to pregnancy. Requirement for resuscitation and/or neonatal intensive care, antenatal and postpartum hemorrhage, retained placenta, postpartum depression and fertility rate were also of interest, but not reported in any identified studies.

Data Extraction
Two authors (S.L. and M.C.) used a standardized data extraction form to extract independently extract data in duplicate. Disagreements were resolved by consensus with C.H.S., E.I.B. or M.E.K. Extracted data included study design, identification, recruitment and characteristics of study participants, inclusion/exclusion criteria, descriptions of interventions and comparators and details of infertility and pregnancy-related outcomes.

Risk of Bias and Certainty of the Evidence
Two authors (S.L. and M.C.) independently assessed risk of bias using the Newcastle-Ottawa Scale (7). Overall quality of evidence was assessed using the GRADE approach and rated as high, moderate, low or very low quality. Observational studies were initially rated low quality but could be upgraded based on large magnitude of effect, judgement that all plausible confounding reduced a demonstrated effect or suggested a spurious effect when results showed no effect, or a dose response gradient (8).

Statistical Analysis
Our primary analysis combined women of all IBD subtypes. Studies comparing women with and without surgery and women with open and laparoscopic surgical procedures were pooled using random-effects meta-analyses. Where possible, we calculated risk ratios (RRs) with 95% confidence interval (CI) to compare outcomes for each comparison. We pooled odds ratios (ORs) instead of RRs using the generic inverse variance method when individual studies reported ORs with corresponding CIs that were adjusted for confounding variables and did not provide contingency tables. Studies comparing women before and after surgery were summarized qualitatively due to concerns about the statistical validity of pooling data without accounting for the paired nature of the data.

We did not construct a funnel plot nor test for funnel plot asymmetry as no analysis included more than 10 studies (8). Analyses were conducted using Review Manager (RevMan) 5.3 (The Cochrane Collaboration).
Sensitivity and Subgroup Analyses
We conducted subgroup analyses based on IBD subtype (CD or UC) and age at surgery (<18 years, 18–34 years, ≥35 years). A sensitivity analysis excluding women with active disease at conception or a diagnosis of IBD during pregnancy or postpartum was also conducted.

RESULTS
Description of Included Studies
Database searching identified 1092 records; 151 underwent full-text review and 16 (all observational) were included (Supplementary Figure S1, Table 1). Ten studies included our prespecified comparisons and were meta-analyzed. Nine compared women with and without previous surgery. One compared open and laparoscopic IPAA. Seven compared the risk of infertility and/or secondary outcomes before and after surgery. One included comparisons of women with and without IPAA and women before and after IPAA. No studies evaluated the impact of perianal surgery on infertility or pregnancy outcomes.

Risk of Bias of Included Studies
The risk of bias of included studies is summarized in Supplementary Figure S2. Overall, studies were at high risk of selection and misclassification bias. Most studies included unadjusted estimates and were at risk of confounding.

Any Previous Surgery Versus No Previous Surgery
Infertility
Previous surgery was not associated with infertility at 12 months (RR 5.45, 95% CI: 0.41 to 72.57; Figure 1). Both studies evaluating this association only included UC patients; one compared women with and without IPAA (9) and the other compared women with and without restorative proctocolectomy with ileorectal anastomosis (10).

One study reported infertility at 24 months was associated with previous surgery (RR 3.59, 95% CI: 1.32 to 9.73) with a significant association in UC patients (RR 5.28, 95% CI: 2.09 to 13.34), but not in CD (RR 2.03, 95% CI: 0.56 to 7.33). No detailed information about surgical procedures was reported (11).

Based on GRADE analyses, the overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Miscarriage
Surgery was associated with miscarriage (OR 2.03, 95% CI: 1.14 to 3.60; Figure 2A). Findings were consistent when limiting the analysis to women with CD (OR 2.56, 95% CI: 1.19 to 5.51) and UC (OR 7.14, 95% CI: 1.02 to 50.18) and in a sensitivity analysis excluding women with active disease at conception (RR 2.38, 95% CI: 1.11 to 5.11; Supplementary Figure S3). Studies evaluating this association did not describe the type of surgery women underwent. The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Stillbirth
Stillbirth and previous IBD surgery were not associated (RR 1.96, 95% CI: 0.42 to 9.18; Figure 2B). Results were consistent in women with CD (RR 1.98, 95% CI: 0.32 to 12.16) and UC (RR 1.91, 95% CI: 0.10 to 36.02). One study presenting data specific to women with quiescent disease reported no events in either group (11) and no association in a second study (RR 1.26, 95% CI: 0.07 to 23.54) (12). These studies did not describe the surgical procedures women underwent. The overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Use of ART
In one study, female UC patients with an IPAA were more likely to use ART (RR 25.09, 95% CI: 1.56 to 403.76) compared to those without. The overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Caesarean Section
The association between previous surgery and caesarean section was reported in one study (RR 2.23, 95% CI: 1.00 to 4.95), which also presented disease-specific associations (CD, RR 3.60, 95% CI: 0.98 to 13.19; UC, RR 1.67, 95% CI: 0.61 to 4.59). All women with UC had IPAA. Women with CD underwent a variety of surgical procedures. The overall certainty of evidence was downgraded from low to very low due to high overall risk of bias.

Prematurity
Preterm birth was not associated with previous surgery (RR 1.91, 95% CI: 0.67 to 5.48; Figure 2C); this was consistent in women with CD (RR 2.32, 95% CI: 0.75 to 7.21) and UC (RR 0.56, 95% CI: 0.03 to 9.73). Results were consistent in an analysis limited to women with remission (RR 1.17, 95% CI: 0.11 to 12.38) (11). In one study, all women with UC who had previous surgery had IPAA while those with CD underwent various surgical procedures. The remaining studies did not describe the surgeries women underwent. The overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Low Birth Weight
One study reported no association between previous surgery and giving birth to a low birthweight infant (RR 0.61, 95% CI: 0.08 to 4.83), with similar findings in women with CD (RR 0.67, 95%
| Study       | Study design        | Years of study | Comparison                                                                 | Type of IBD | Outcomes                                      |
|------------|---------------------|----------------|-----------------------------------------------------------------------------|-------------|-----------------------------------------------|
| Banks 1957 | Retrospective cohort | 1931–1950      | Previous surgery vs. no previous surgery                                     | UC          | Miscarriage                                   |
|            |                     |                |                                                                             |             | Stillbirth                                    |
| Bartels 2012 | Cross-sectional     | 2010–2011 (surgery: 1993–2009) | Open vs. laparoscopic IPAA                                                  | UC          | Infertility (12 months)                        |
| Bortoli 2011 | Prospective cohort  | 2003–2006      | Previous surgery vs. no previous surgery                                     | CD          | Miscarriage                                   |
| Gorgun 2004 | Cross-sectional     | 1983–2011      | Before and after restorative proctocolectomy with IPAA                      | UC          | Infertility (12 months)                        |
|            |                     |                |                                                                             |             | Use of ART                                    |
| Hahnloser 2004 | Cross-sectional    | 1981–1995      | Before and after IPAA                                                        | UC          | Miscarriage                                   |
|            |                     |                |                                                                             |             | Stillbirth                                    |
|            |                     |                |                                                                             |             | Gestational diabetes                          |
|            |                     |                |                                                                             |             | Preeclampsia                                  |
|            |                     |                |                                                                             |             | Infertility (24 months)                        |
| Hudson 1997 | Cross-sectional     | 1967–1986      | Previous surgery vs. no previous surgery                                     | CD, UC      | Miscarriage                                   |
|            |                     |                |                                                                             |             | Stillbirth                                    |
| Johnson 2004 | Cross-sectional    | Unknown        | IPAA vs. no previous surgery                                                 | UC          | Infertility (12 months)                        |
|            |                     |                | Before and after IPAA                                                        |             | Use of ART                                    |
| Koivusalo 2009 | Cross-sectional    | 1985–2005      | Restorative proctocolectomy with ileoanal anastomosis vs. no previous surgery | UC          | Infertility (12 months)                        |
| Mortier 2006 | Cross-sectional    | 2003 (surgery: 1962–1999) | Before and after total colectomy with ileorectal anastomosis               | UC          | Infertility (6, 12, 24 months)                 |
|            |                     |                |                                                                             |             | Time to pregnancy                             |
| Moser 2000  | Retrospective cohort | 1993–1997      | Previous surgery vs. no previous surgery                                     | CD          | Small for gestational age                      |
| Naganuma 2011 | Cross-sectional    | 1989–2008      | Previous surgery vs. no previous surgery                                     | IBD         | Miscarriage                                   |
| Nielsen 1984 | Retrospective cohort | 1968–1980      | Previous surgery vs. no previous surgery                                     | CD          | Miscarriage                                   |
|            |                     |                |                                                                             |             | Stillbirth                                    |
|            |                     |                |                                                                             |             | Preterm birth                                 |
| Olsen 2002  | Prospective cohort  | 1982–1998      | Before and after restorative proctocolectomy with IPAA                      | UC          | Infertility (12, 24 months)                    |
| Ravid 2002  | Cross-sectional     | 1982–1998      | Before and after IPAA                                                        | UC          | Miscarriage                                   |
|            |                     |                |                                                                             |             | Stillbirth                                    |
|            |                     |                |                                                                             |             | Caesarean section                             |
|            |                     |                |                                                                             |             | Miscarriage                                   |
|            |                     |                |                                                                             |             | Use of ART                                    |
| Tulchinsky 2013 | Cross-sectional    | Not specified | Before and after restorative proctocolectomy                                | UC          | Miscarriage                                   |
|            |                     |                |                                                                             |             | Caesarean section                             |
| Zavorova 2017 | Retrospective cohort | 2014–2016      | Previous surgery vs. no previous surgery                                     | CD, UC      | Miscarriage                                   |
|            |                     |                |                                                                             |             | Low birth weight                              |
|            |                     |                |                                                                             |             | Very low birth weight                         |
|            |                     |                |                                                                             |             | Prematurity                                   |

ART, Assisted reproductive technology; CD, Crohn’s disease; IBD, Inflammatory bowel disease; IPAA, Ileal pouch-anal anastomosis; UC, Ulcerative colitis.
CI: 0.03 to 13.60) and UC (RR 0.56, 95% CI: 0.03 to 9.73). No infants were very low birth weight. All women with UC requiring surgery underwent IPAA. Women with CD underwent a variety of procedures. The overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Small for Gestational Age
In women with CD, one study demonstrated no association between previous surgery and small for gestational age infants (RR 2.54, 95% CI: 0.80 to 8.01). Details of the surgical procedure(s) required were not provided. The overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Laparoscopic Versus Open Surgery
Infertility
One study reported no difference in the risk of infertility at 12 months in women with UC who underwent laparoscopic versus open surgery (RR 0.70, 95% CI: 0.38 to 1.27). All women in this study underwent IPAA. The overall certainty of evidence was downgraded from low to very low due to high risk of bias and imprecise estimates.

Before and After Surgery
Infertility
The rates of infertility at 6, 12 and 24 months in women before and after surgery were described in one, five and two studies, respectively (Table 2). Infertility at 12 months was reported in 20.8% (68/327) of women before surgery compared to 63.4% (239/277) of women afterwards. Similar proportions reported infertility at 6 and 24 months. Age-stratified comparisons from a single study suggested rates of infertility were similar before and after surgery in women who were younger at the time of surgery, with larger differences noted in women who were older at surgery (Supplementary Table S1) (13). The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Miscarriage
Three studies reported miscarriage rates before and after surgery in females with UC; miscarriage occurred in 15.4% (19/123) of pregnancies before and 15.7% (21/134) of pregnancies after surgery (Table 3). The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Stillbirth
In two studies, 5.3% (2/38) of pregnancies in women with UC before IPAA resulted in stillbirth compared to 3.8% (3/80) of pregnancies after IPAA (Table 3). The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Use of ART
Three studies observed use of ART before and after surgery in female UC patients (Table 4). Results from these studies are not directly comparable because the types of patients considered ‘at risk’ for using ART differed between studies. In one study, 5.3% (5/95) of women attempting pregnancy used ART before surgery compared to 30.3% (20/66) after surgery (9). Among women who were infertile following 12 months of attempted pregnancy, 42.2% (19/45) used ART before surgery compared to 51.4% (36/70) after surgery (13). In the final study, 8.6% (6/70) of pregnancies before restorative proctocolectomy occurred in women using ART compared to 34.3% (11/32) of pregnancies occurring after surgery (14). The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Caesarean Section
Two studies described delivery by caesarean section before and after surgery in females with UC; 11.0% (8/73) of infants were delivered via caesarean section before surgery compared to 48.0% (36/75) after surgery (Table 3). The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Gestational Diabetes and Preeclampsia
One study reported gestational diabetes and preeclampsia before and after surgery. Among female UC patients with pregnancies both before and after surgery, 8.1% (3/37)
developed gestational diabetes and 5.4% (2/37) had pre-eclampsia before surgery. None experienced either condition in pregnancies after surgery. The overall certainty of evidence for both outcomes was downgraded from low to very low due to high risk of bias.

### Time to Pregnancy

Two studies observed time to pregnancy before and after surgery among women with UC (Table 5). One reported a median (range) time of 2 (1 to 3) months to pregnancy in five women before total colectomy with ileorectal anastomosis.
compared to 5 (2 to 36) months in 15 women attempting pregnancy after surgery (15). The second reported a mean (SD) of 5.0 (11.6) months to pregnancy before restorative proctocolectomy; pregnancy occurred immediately in 32/70 pregnancies (26 women) (14). After surgery, the mean time to pregnancy was 16.3 (25.1) months; 17 of 27 women successfully conceived a total of 32 times. The overall certainty of evidence was downgraded from low to very low due to high risk of bias.

Table 2. Infertility in female patients with ulcerative colitis before and after surgery

| Type of surgery                                    | Study                           | Before surgery | After surgery |
|----------------------------------------------------|---------------------------------|----------------|----------------|
|                                                    |                                 | Infertile, n (%) | Total, n     | Infertile, n (%) | Total, n     |
| Infertility at 12 months                           |                                 |                |                |                |                |
| Restorative proctocolectomy with IPAA             | Gorgun 2004 (13)                | 45 (38.5)      | 117            | 70 (58.3)      | 120            |
| IPAA                                               | Olsen 2002 (35)                 | 18 (21.4)      | 84             | 122 (81.9)     | 149            |
| Total colectomy with ileorectal anastomosis       | Johnson 2004 (9)               | 4 (4.2)        | 95             | 29 (43.9)      | 66             |
| Restorative proctocolectomy                        | Mortier 2006 (15)              | 1 (20.0)       | 5              | 8 (53.3)       | 15             |
| Total                                              | Tulchinsky 2013 (14)           | 0 (0.0)        | 26             | 10 (37.0)      | 27             |
|                                                    | Total                           | 68 (20.8)      | 327            | 239 (63.4)     | 377            |
| Infertility at 6 months                            |                                 |                |                |                |                |
| Total colectomy with ileorectal anastomosis       | Mortier 2006 (15)              | 1 (20.0)       | 5              | 9 (60.0)       | 15             |
| Infertility at 24 months                           |                                 |                |                |                |                |
| Restorative proctocolectomy with IPAA             | Olsen 2002 (35)                | 13 (15.5)      | 84             | 108 (72.5)     | 149            |
| Total colectomy with ileorectal anastomosis       | Mortier 2006 (15)              | 1 (20.0)       | 5              | 7 (46.7)       | 15             |
|                                                    | Total                           | 14 (15.7)      | 89             | 115 (70.1)     | 164            |

Table 3. Outcomes of pregnancy in female patients with ulcerative colitis before and after surgery

| Type of surgery                                    | Study                           | Before surgery | After surgery |
|----------------------------------------------------|---------------------------------|----------------|----------------|
|                                                    |                                 | Miscarriage, n (%) | Total, n     | Miscarriage, n (%) | Total, n     |
| Miscarriage                                        |                                 |                |                |                |                |
| IPAA                                               | Hahnloser 2004 (31)             | 10 (27.0)      | 37             | 6 (16.2)       | 37             |
| Restorative proctocolectomy                        | Ravid 2002 (36)                | 1 (6.3)        | 16             | 9 (13.8)       | 65             |
|                                                   | Tulchinsky 2013 (14)            | 8 (11.4)       | 70             | 6 (18.8)       | 32             |
|                                                   | Total                           | 19 (15.4)      | 123            | 21 (15.7)      | 134            |
| Stillbirth                                          |                                 |                |                |                |                |
| IPAA                                               | Hahnloser 2004 (31)             | 2 (7.4)        | 27             | 2 (6.5)        | 31             |
| Restorative proctocolectomy                        | Ravid 2002 (36)                | 0 (0)          | 11             | 1 (2.0)        | 49             |
|                                                   | Total                           | 2 (5.3)        | 38             | 3 (3.8)        | 80             |
| Caesarean section                                  |                                 |                |                |                |                |
| IPAA                                               | Ravid 2002 (36)                | 0 (0)          | 11             | 24 (49.0)      | 49             |
| Restorative proctocolectomy                        | Tulchinsky 2013 (14)            | 8 (12.9)       | 62             | 12 (46.2)      | 26             |
|                                                   | Total                           | 8 (11.0)       | 73             | 36 (48.0)      | 75             |

Discussion

Based on available data, it is uncertain if previous IBD-related surgery is associated with infertility and pregnancy outcomes in women with IBD, or if differences in infertility exist between women with UC who underwent laparoscopic and open IPAA. Our conclusions are based on very low-quality evidence due to the observational nature of the data, limited number of studies, small sample sizes and high risk of bias. Thus, our findings should be interpreted with caution.
Notably, our findings differed from two systematic reviews that concluded infertility was more common in women with IPAA than those without (2,3). Our conclusions likely differed from these reviews due to different methodology—we only included studies that rigorously defined infertility (i.e., an inability to become pregnant within a prespecified amount of time without using birth control). This ensured equal follow-up time among all women regardless of surgical history and was not distorted by differing rates of voluntary infertility or other characteristics among women with and without previous surgery (e.g., disease severity). Infertility estimates can vary drastically when using different definitions, resulting in different conclusions when comparing rates between groups (16). Secondly, we did not meta-analyze studies assessing infertility in women before and after IPAA construction due to concerns about the statistical validity of not accounting for repeated observations and residual confounding by age. In a comparison of age-specific infertility estimates before and after IPAA, no differences in infertility were observed among women undergoing surgery before 30 while infertility rates were higher when IPAA occurred after 30 (13)—an age after which fertility begins to decline more rapidly than at previous ages (17). Consequently, we cannot be certain if there is a true association between IPAA and infertility or if the finding is observed due to the uncontrolled effect of age. Increased infertility observed among women with familial adenomatous polyposis following IPAA (18) may have resulted from the same biases identified in studies of women with IBD.

We originally intended to evaluate the impact of specific surgical interventions on infertility and pregnancy-related outcomes. However, no two studies provided sufficient details of the types of surgery women required or evaluated the same surgical procedure. Further, many studies grouped multiple procedures (i.e., compared any previous IBD-related surgery to those without surgery) and no studies compared women with and without a stoma. Consequently, we are unable to evaluate procedure-specific conclusions about the impact of surgery on infertility. Since variation across surgery types is likely, the applicability of our findings for women considering IBD-related intestinal resection is limited. For example, IPAA construction is more likely to result in fallopian tube damage compared to limited small bowel resection (19, 20). Tubal factors contribute to infertility more often among women with an IPAA (21). Other procedures may be less likely to have a similar impact on

Table 4. Use of assisted reproductive technology in female patients with ulcerative colitis before and after surgery

| Type of surgery                              | Study     | Before surgery | After surgery |
|----------------------------------------------|-----------|----------------|---------------|
|                                              |           | Use of ART, n (%) | Total, n | Use of ART, n (%) | Total, n |
| IPAA                                         | Johnson 2004 (9) | 5 (5.3) | 95 | 20 (30.3) | 66 |
| Restorative proctocolectomy with IPAA        | Gorgun 2004 (13) | 19 (42.2) | 45 | 36 (51.4) | 70 |
| Restorative proctocolectomy                  | Tulchinsky 2013 (14) | 6 (8.6) | 70 | 11 (34.3) | 32 |

ART, Assisted reproductive technology; IPAA, Ileal pouch-anal anastomosis.

*Number of women attempting pregnancy.

+Number of women infertile following 12 months of attempting pregnancy.

—Number of pregnancies in which women used ART.

Table 5. Time to pregnancy in female patients with ulcerative colitis before and after surgery, measured in months

| Type of surgery                              | Study     | Measure | Before surgery | Number of women attempting pregnancy | After surgery | Number of women attempting pregnancy |
|----------------------------------------------|-----------|---------|----------------|--------------------------------------|---------------|--------------------------------------|
|                                              |           |         | Time to pregnancy |                                      |               |                                      |
| Total colectomy with ileorectal anastomosis  | Mortier 2006 (15) | Median (range) | 2 (1–3) | 5 | 5 (2–36) | 15 |
| Restorative proctocolectomy                  | Tulchinsky 2013 (14) | Mean (SD) | 5.0 (11.6) | 26 (70 pregnancies*) | 16.3 (25.1) | 27* (32 pregnancies) |

SD, Standard deviation.

*Pregnancy occurred ‘immediately’ in 32 pregnancies.

*17/27 women successfully conceived.
fallopian tubes. Further, variations may exist across pouch types (e.g., J, S or Kock pouches) and surgical techniques. One small study reported a numeric increase in adhesions among women who underwent three-stage versus two-stage IPAA construction, which may subsequently impact infertility (22), while another reported numeric increases in infertility among those with a stapled anastomosis compared to those with a hand-sewn anastomosis (23).

Prior studies have suggested sexual dysfunction is more common in women with IBD than in the general population and may be further increased in women who have had previous IBD surgery, although findings have been inconsistent (24, 25). Impaired sexual function may also contribute to involuntary infertility and studies evaluating infertility in women with IBD must consider the relative contributions of voluntary and involuntary infertility.

Very-low-quality evidence suggests caesarean section may be more likely in women with prior IBD-related surgery compared to women without. However, insufficient information was available to determine if this association reflected physician and patient preference or obstetric indications. A survey of Canadian gastroenterologists reported very little consensus regarding the impact of mode of delivery among women with IPAA (26). Recently published clinical practice guidelines recommend caesarean section for women with IPAA due to concerns about pouch function and sphincter injury after vaginal delivery (27), but were based on limited evidence. The guidelines also recommend women with active perianal disease deliver by caesarean section. For all other women with IBD, regardless of surgical history, vaginal delivery is recommended unless there are obstetric reasons for caesarean section (27). Increasing evidence points to the safety of vaginal delivery for women without IPAA or active perianal disease, despite earlier concerns that vaginal delivery might increase the risk of perianal disease (28).

In conclusion, there is limited information about the impact of IBD-related surgery on the risk of female infertility. Although there were associations between IBD-related surgery and some secondary outcomes (miscarriage, use of ART, caesarean section and low birth weight), these findings were based on very-low-quality evidence from studies with small sample sizes that did not account for other disease-related factors (e.g., disease activity). To better evaluate how surgery impacts female infertility and pregnancy outcomes, well-designed, large, prospective cohort studies with detailed information on IBD disease activity and phenotype, medical and surgical treatment and attempted pregnancies and outcomes are needed. Health care providers should counsel women that the risk of infertility after intra-abdominal surgery may be increased; additionally, patients should be aware that the existing research is of poor quality and limited quantity.

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

Acknowledgments
The review authors would like to thank Takashi Ishige for translating an article that was written in Japanese.

G.G.K. is a Canadian Institutes of Health Research (CIHR) Embedded Clinician Research Chair. A.M. is supported by a New Investigator Award from CIHR, Canadian Association of Gastroenterology (CAG) and Crohn’s and Colitis Canada (CCC). E.I.B. is supported by a New Investigator Award from CIHR, CAG and CCC. E.I.B. is also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program. MEK is supported by a Post-Doctoral Fellowship from CIHR, CAG and CCC. Funding for the Cochrane IBD Group (May 1, 2017 to April 30, 2022) has been provided by CCC.

Author Contributions Designing the review: M.C., S.L., C.H.S., G.G.K., A.M., E.I.B. and M.E.K. Coordinating the review: C.H.S., E.I.B. and M.E.K. Developing the search strategy: M.C., C.H.S., E.I.B. and M.E.K. Collecting data: S.L. and M.C. Performing the literature search: M.C. and M.E.K. Selecting papers for full review: S.L., M.C., C.H.S., E.I.B. and M.E.K. Obtaining papers for review: M.C. and M.E.K. Screening papers for inclusion in the review: S.L., M.C., C.H.S., E.I.B. and M.E.K. Assessing the quality of papers: S.L. and M.C. Extracting data from papers: S.L. and M.C. Managing data: S.L., M.C. and M.E.K. Entering data into RevMan software: S.L. and M.C. Analyzing data: S.L., M.C. and M.E.K. Interpreting data: S.L., M.C., C.H.S., P.G.K., G.G.K., A.M., A.R., E.I.B. and M.E.K. Providing a methodological perspective: C.H.S., P.G.K., G.G.K., A.M., A.R., E.I.B. and M.E.K. Writing the review: S.L., M.C., C.H.S., M.E.K. and E.I.B. Critically revising the manuscript: S.L., M.C., C.H.S., P.G.K., G.G.K., A.M., A.R., E.I.B. and M.E.K. Critically revising the manuscript: S.L., M.C., C.H.S., P.G.K., G.G.K., A.M., A.R., E.I.B. and M.E.K. Made equal contributions to this manuscript and are both senior authors.

Funding Funding for the Cochrane IBD Group (May 1, 2017 to April 30, 2022) has been provided by Crohn’s and Colitis Canada.

Conflict of Interest C.H.S. has served as a consultant and on advisory boards for Janssen Pharmaceuticals, Abbvie, Takeda, Actavis, Ferring, Shire and Pfizer. She has received an educational grant through Janssen Pharmaceuticals. C.H.S. has also provided lectures for Janssen Pharmaceuticals, Abbvie, Ferring, Shire and Takeda. P.G.K. has received speaking and consultancy honoraria from Abbvie, Janssen, Pfizer, Takeda and UCB. G.G.K. has received honoraria for speaking or consultancy from Abbvie, Janssen, Pfizer and Takeda. He has received research support from Janssen, Abbvie, GlaxoSmith Kline, Merck and Shire. He shares ownership of a patent: TREATMENT OF INFLAMMATORY DISORDERS, AUTOIMMUNE DISEASE AND PBC. UTI Limited Partnership, assignee. Patent 62/ 555,397. September 7, 2017. S.L., M.C., A.M., A.R., E.I.B. and M.E.K. have no known conflicts of interest.
References

1. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. Gastroenterology 2013;145(5):996–1006.

2. Rajaratnam SG, Eglinton TW, Hider P, et al. Impact of ileal pouch-anal anastomosis on female fertility: Meta-analysis and systematic review. Int J Colorectal Dis 2011;26(11):1365–74.

3. Waljee A, Waljee J, Morris AM, et al. Threefold increased risk of infertility: A meta-analysis after ileal pouch anal anastomosis in ulcerative colitis. Gut 2006;55(11):1575–80.

4. Lee S, Crowe M, Seow CH, et al. The impact of surgical therapies for inflammatory bowel disease on female fertility. Cochrane Database Syst Rev 2019;7:CD012711.

5. Crowe M, Lee S, Seow CH, et al. The impact of surgical therapies for inflammatory bowel disease on female fertility (protocol). Cochrane Database Syst Rev 2017;(7):CD012711. doi:10.1002/14651858.CD012711.

6. Moher D, Liberati A, Tetzlaff J, et al.; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6(7):e1000097.

7. Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. ohri.ca. http://www.cochrane.ca/programs/clinical_epidemiology/oxford.asp. Accessed January 30, 2017.

8. Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd, 2008.

9. Johnson P, Richard C, Ravid A, et al. Female infertility after ileal pouch-anal anastomosis: A population based case-control study. Br J Surg 2006;93(11):1575–80.

10. Koivusalo A, Pakarinen MP, Natunen J, et al. Sexual functions in adulthood after proctocolectomy with ileal pouch-anal anastomosis. Int J Colorectal Dis 2001;16(4):211–5.

11. Hudson M, Flett G, Sinclair TS, et al. Fertility and pregnancy in inflammatory bowel disease. Int J Gynaecol Obstet 1997;58(2):229–37.

12. Banks BM, Korelitz BI, Zetzel L. The course of nonspecific ulcerative colitis: Review of twenty years’ experience and late results. Gastroenterology 1957;32(6):983–1012.

13. Gorgun E, Remzi FH, Goldberg JM, et al. Fertility is reduced after restorative proctocolectomy for inflammatory bowel disease: Prospective European case-control ECCO-EpiCom study, 2003–2006. Aliment Pharmacol Ther. 2011;34(7):724–34. doi:10.1111/j.1365-2036.2011.04794.x.

14. Hahlooser D, Pemberton JH, Wolf BG, et al. Pregnancy and delivery before and after ileal pouch-anal anastomosis for inflammatory bowel disease: Immediate and long-term consequences and outcomes. Dis Colon Rectum 2004;47(7):1119–26.

15. Moser MA, Okun NB, Mayes DC, et al. Crohn’s disease, pregnancy, and birth weight. Am J Gastroenterol 2000;95(4):1021–6.

16. Nielsen OH, Andresson B, Bondesen S, et al. Pregnancy in inflammatory bowel disease: An interdisciplinary clinical challenge. Am J Obstet Gynecol. 2016;215(1):58–62. doi:10.1016/j.ajog.2016.01.188.

17. Nordling K, Olander J, Nutser M, et al. Conception and pregnancy outcome in women with inflammatory bowel disease: A multicentre study from Japan. J Crohns Colitis 2011;5(4):317–23.

18. Nielsen OH, Andresson B, Bondesen S, et al. Pregnancy in Crohn’s disease. Scand J Gastroenterol 1984;19(6):724–32.

19. Oresland T, Palmblad S, Ellstrom M, et al. Gynaecological and sexual function related to anatomical changes in the female pelvis after restorative proctocolectomy. Int J Colorectal Dis 1994;9(2):77–81.

20. Auströy M, Palmblad S, Wikland M, et al. Radiological study of changes in the pelvis in women following proctocolectomy. Int J Colorectal Dis 1991;6(2):103–7.

21. Pabby V, Oza SS, Dodge LE, et al. In vitro fertilization is successful in women with ulcerative colitis and ileal pouch anal anastomosis. Am J Gastroenterol 2015;110(6):792–7.

22. Hull TL, Joyce MB, Geisler DP, et al. Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis. Br J Surg 2012;99(2):270–5.

23. Harnoy Y, Desfournes V, Bouguen G, et al. Sexuality and fertility outcomes after hand sewn versus stapled ileal pouch anal anastomosis for ulcerative colitis. J Surg Res 2016;200(1):66–72.

24. Eluri S, Cross RK, Martin C, et al. Inflammatory bowel diseases can adversely impact domains of sexual function such as satisfaction with sex life. Dig Dis Sci. 2018;63(6):1572–82. doi:10.1007/s10620-018-0211-8.

25. Sanders JN, Gawron LM, Friedman S. Sexual satisfaction and inflammatory bowel diseases: An interdisciplinary clinical challenge. Am J Obstet Gynecol. 2016;215(1):58–62. doi:10.1016/j.ajog.2016.01.188.

26. Kuenzig E, Mathivanan M, Seow C, et al. Gastroenterologists differ in their preferred mode of delivery for pregnant women with ileal-pouch-anal anastomosis. J Can Assoc Gastroenterol 2018;1(Suppl 2):236–7. doi:10.1007/s13109-018-0236-7.

27. Nguyen GC, Seow CH, Maxwell C, et al.; IBD in Pregnancy Consensus Group; Canadian Association of Gastroenterology. The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. Gastroenterology 2016;150(3):734–57.e1.

28. Foulon A, Dupas JL, Sabbagh C, et al. Defining the most appropriate delivery mode in women with inflammatory bowel disease: A systematic review. Inflamm Bowel Dis 2017;23(5):712–20.

29. Bartels SAL, D’Hoore A, Cuesta MA, Bensdorp AJ, Lucas C, Benelman WA. Significantly increased pregnancy rates after laparoscopic restorative proctocolectomy. Ann Surg 2012;256(6):1045–8. doi:10.1097/SLA.0b013e318250ca99.

30. Bortoli A, Pedersen N, Duricova D, et al. Pregnancy outcome in inflammatory bowel disease: Prospective European case-control ECCO-EpiCom study, 2003–2006. Aliment Pharmacol Ther. 2011;34(7):724–34. doi:10.1111/j.1365-2036.2011.04794.x.

31. Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: A systematic review and meta-analysis of population-based studies. Gastroenterology 2013;145(5):996–1006.