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[Intervention Review]

The impact of surgical therapies for inflammatory bowel disease on female fertility

Sangmin Lee¹, Megan Crowe², Cynthia H Seow³, Paulo G Kotze⁴, Gilaad G Kaplan³, Amy Metcalfe⁵, Amanda Ricciuto⁶, Eric I Benchimol^{7,8}, M Ellen Kuenzig⁷

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

Contact address: Eric I Benchimol, Division of Gastroenterology Hepatology & Nutrition, The Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, ON, K1H 8L1, Canada. ebenchimol@cheo.on.ca.

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ABSTRACT

Background

Women with inflammatory bowel disease (IBD) may require surgery, which may result in higher risk of infertility. Restorative proctocolectomy with ileal anal pouch anastomosis (IPAA) may increase infertility, but the degree to which IPAA affects infertility remains unclear, and the impact of other surgical interventions on infertility is unknown.

Objectives

Primary objective

- To determine the effects of surgical interventions for IBD on female infertility.

Secondary objectives

- To evaluate the impact of surgical interventions on the need for assisted reproductive technology (ART), time to pregnancy, miscarriage, stillbirth, prematurity, mode of delivery (spontaneous vaginal, instrumental vaginal, or Caesarean section), infant requirement for resuscitation and neonatal intensive care, low and very low birth weight, small for gestational age, antenatal and postpartum hemorrhage, retained placenta, postpartum depression, gestational diabetes, and gestational hypertension/preeclampsia.

Search methods

We searched MEDLINE, Embase, CENTRAL, and the Cochrane IBD Group Specialized Register from inception to September 27, 2018, to identify relevant studies. We also searched references of relevant articles, conference abstracts, grey literature, and trials registers.

Selection criteria

We included observational studies that compared women of reproductive age (≥ 12 years of age) who underwent surgery to women with IBD who had a different type of surgery or no surgery (i.e. treated medically). We also included studies comparing women before and after surgery. Any type of IBD-related surgery was permitted. Infertility was defined as an inability to become pregnant following 12 months

of unprotected intercourse. Infertility at 6, 18, and 24 months was included as a secondary outcome. We excluded studies that included women without IBD and those comparing women with IBD to women without IBD.

Data collection and analysis

Two review authors independently screened studies and extracted data. We used the Newcastle-Ottawa Scale to assess bias and GRADE to assess the overall certainty of evidence. We calculated the pooled risk ratio (RR) and 95% confidence interval (CI) using random-effects models. When individual studies reported odds ratios (ORs) and did not provide raw numbers, we pooled ORs instead.

Main results

We identified 16 observational studies for inclusion. Ten studies were included in meta-analyses, of which nine compared women with and without a previous IBD-related surgery and the other compared women with open and laparoscopic IPAA. Of the ten studies included in meta-analyses, four evaluated infertility, one evaluated ART, and seven reported on pregnancy-related outcomes. Seven studies in which women were compared before and after colectomy and/or IPAA were summarized qualitatively, of which five included a comparison of infertility, three included the use of ART, and three included other pregnancy-related outcomes. One study included a comparison of women with and without IPAA, as well as before and after IPAA, and was therefore included in both the meta-analysis and the qualitative summary. All studies were at high risk of bias for at least two domains.

We are very uncertain of the effect of IBD surgery on infertility at 12 months (RR 5.45, 95% CI 0.41 to 72.57; 114 participants; 2 studies) and at 24 months (RR 3.59, 95% CI 1.32 to 9.73; 190 participants; 1 study). Infertility was lower in women who received laparoscopic surgery compared to open restorative proctocolectomy at 12 months (RR 0.70, 95% CI 0.38 to 1.27; 37 participants; 1 study).

We are very uncertain of the effect of IBD surgery on pregnancy-related outcomes, including miscarriage (OR 2.03, 95% CI 1.14 to 3.60; 776 pregnancies; 5 studies), use of ART (RR 25.09, 95% CI 1.56 to 403.76; 106 participants; 1 study), delivery via Caesarean section (RR 2.23, 95% CI 1.00 to 4.95; 20 pregnancies; 1 study), stillbirth (RR 1.96, 95% CI 0.42 to 9.18; 246 pregnancies; 3 studies), preterm birth (RR 1.91, 95% CI 0.67 to 5.48; 194 pregnancies; 3 studies), low birth weight (RR 0.61, 95% CI 0.08 to 4.83), and small for gestational age (RR 2.54, 95% CI 0.80 to 8.01; 65 pregnancies; 1 study).

Studies comparing infertility before and after IBD-related surgery reported numerically higher rates of infertility at six months (before: 1/5, 20.0%; after: 9/15, 60.0%; 1 study), at 12 months (before: 68/327, 20.8%; after: 239/377, 63.4%; 5 studies), and at 24 months (before: 14/89, 15.7%; after: 115/164, 70.1%; 2 studies); use of ART (before: 5.3% to 42.2%; after: 30.3% to 34.3%; proportions varied across studies due to differences in which women were identified as at risk of using ART); and delivery via Caesarean section (before: 8/73, 11.0%; after: 36/75, 48.0%; 2 studies). In addition, women had a longer time to conception after surgery (two to five months; 2 studies) than before surgery (5 to 16 months; 2 studies). The proportions of women experiencing miscarriage (before: 19/123, 15.4%; after: 21/134, 15.7%; 3 studies) and stillbirth (before: 2/38, 5.3%; after: 3/80, 3.8%; 2 studies) were similar before and after surgery. Fewer women experienced gestational diabetes after surgery (before: 3/37, 8.1%; after: 0/37; 1 study), and the risk of preeclampsia was similar before and after surgery (before: 2/37, 5.4%; after: 0/37; 1 study). We are very uncertain of the effects of IBD-related surgery on these outcomes due to poor quality evidence, including confounding bias due to increased age of women after surgery.

We rated evidence for all outcomes and comparisons as very low quality due to the observational nature of the data, inclusion of small studies with imprecise estimates, and high risk of bias among included studies.

Authors' conclusions

The effect of surgical therapy for IBD on female infertility is uncertain. It is also uncertain if there are any differences in infertility among those undergoing open versus laparoscopic procedures. Previous surgery was associated with higher risk of miscarriage, use of ART, Caesarean section delivery, and giving birth to a low birth weight infant, but was not associated with risk of stillbirth, preterm delivery, or delivery of a small for gestational age infant. These findings are based on very low-quality evidence. As a result, definitive conclusions cannot be made, and future well-designed studies are needed to fully understand the impact of surgery on infertility and pregnancy outcomes.

PLAIN LANGUAGE SUMMARY

The risk of infertility in women with IBD who have had surgery

What is inflammatory bowel disease?

There are two types of inflammatory bowel disease (IBD): Crohn's disease and ulcerative colitis. IBD is a lifelong disease of the digestive system. Patients with IBD can experience diarrhea, abdominal pain, and fatigue, among other symptoms. IBD is most often diagnosed in teenagers and young adults, around the time of family planning decisions. Previous studies have suggested that women who have undergone surgery to remove their colon and create an ileal anal pouch anastomosis (IPAA or J-pouch) may have trouble getting pregnant. This type of surgery is common in women with ulcerative colitis when medications do not work. The impact that other types of IBD surgeries can have on a woman's ability to become pregnant is unknown.

What types of surgery do people with IBD require?

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When medication fails, a person with IBD may require surgery to remove part of the intestine or colon, which can result in the need for an ostomy - an opening in the skin created to allow drainage of fecal matter into a collection bag outside the body. An additional surgery that patients with ulcerative colitis may have is an IPAA, also called a J-pouch. This procedure creates a reservoir using part of the small intestine, which allows the ostomy to be closed. People with Crohn's disease may also have their colon removed. However, people with Crohn's disease rarely receive a J-pouch because the pouch often becomes inflamed. Additionally, people with Crohn's disease may have part of their small intestine removed or a strictureplasty to widen the intestine where it has become narrowed because of scarring. These surgeries can be performed via a laparoscopic approach or an open approach. In laparoscopic surgery, cameras and tools are inserted through small incisions and a slightly larger incision is made to remove the diseased portion of the intestine. In open surgery, a single large cut is made in the abdomen, allowing the surgeon to directly see and remove the diseased portions of bowel.

What did researchers investigate?

Researchers reviewed the literature to identify previous studies that reported the risk of infertility in women with IBD who had previous IBD-related surgeries as well as studies that reported the impact of previous surgery on pregnancy outcomes (miscarriage, stillbirth, prematurity, low birth weight, and small for gestational age) or pregnancy complications (gestational diabetes, gestational hypertension, postpartum depression, and bleeding).

What did researchers find?

Researchers found 16 studies that reported the impact of surgery on infertility or pregnancy outcomes in women with IBD. Nine studies compared women with and without previous surgery. Four of these studies reported on the impact of surgery on a woman's ability to become pregnant. We were unable to reach conclusions about the association between surgery and infertility because of the low quality of evidence from these studies. Eight reported on pregnancy outcomes and complications. Evidence from these studies was also of very low quality, and we are unable to draw conclusions about the impact of IBD surgery on pregnancy outcomes. Evidence from the one study comparing infertility among women undergoing open and laparoscopic surgery was also of low quality. Thus, we could not draw conclusions about the impact of open and laparoscopic procedures on infertility. The remaining six studies compared women before and after surgery. One study that compared women with IBD who did and did not have surgery also compared women before and after surgery. These seven studies comparing women before and after surgery provided low-quality evidence on differences in women's ability to get pregnant and on outcomes of pregnancy before and after surgery.

Conclusions

Studies on the impact of IBD-related surgery on a woman's ability to get pregnant and on the outcomes of pregnancy are rare and of low quality. As a result, information reviewed in the present study on associations between IBD-related surgery and adverse pregnancy outcomes has high risk of bias, and we have very little confidence in these conclusions. Our results should be interpreted with caution. Additional well-designed studies on this topic are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Any previous surgery compared to no previous surgery for inflammatory bowel disease on female infertility

Risk of infertility and pregnancy outcomes among women who did and did not undergo previous IBD surgery

Patient or population: females with inflammatory bowel disease

Setting: outpatient

Intervention: previous IBD surgery

Comparison: no previous IBD surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of women/pregnancies (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no previous surgery	Risk with any previous IBD surgery				
Infertility at 12 months	Study population		RR 5.45 (0.41 to 72.57)	114 women (2 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}	
	47 per 1000	253 per 1000 (19 to 1000)				
Infertility at 24 months	Study population		RR 3.59 (1.32 to 9.73)	106 women (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b}	
	83 per 1000	297 per 1000 (109 to 805)				
Miscarriage	Study population		OR 2.03 (1.14 to 3.60)	776 pregnancies (5 observational studies)	⊕⊕⊕⊕ Very low ^a	
	69 per 1000 ^c	130 per 1000 (78 to 210)				
Stillbirth	Study population		RR 1.96 (0.42 to 9.18)	246 pregnancies (3 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}	
	20 per 1000	39 per 1000 (8 to 184)				
Use of ART	Study population		RR 25.09 (1.56 to 403.76)	106 women (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b}	We were unable to calculate absolute effects: 20 out of 66 women with previous surgery used
	See comment	See comment				

ART compared to 0 out of 40 women with no previous surgery

Caesarean section	Study population		RR 2.23 (1.00 to 4.95)	20 pregnancies (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b}
	308 per 1000	686 per 1000 (308 to 1000)			
Preterm delivery	Study population		RR 1.91 (0.67 to 5.48)	194 pregnancies (3 observational studies)	⊕⊕⊕⊕ Very low ^{a,b}
	52 per 1000	98 per 1000 (35 to 282)			
Low birth weight	Study population		RR 0.61 (0.08 to 4.83)	19 pregnancies (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b}
	154 per 1000	94 per 1000 (12 to 743)			
Small for gestational age	Study population		RR 2.54 (0.80 to 8.01)	65 (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b}
	125 per 1000	318 per 1000 (100 to 1000)			

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ART: assisted reproductive technology; CI: confidence interval; IBD: inflammatory bowel disease; OR: odds ratio; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded due to high overall risk of bias.

^bDowngraded due to imprecise estimates.

^cRisk of miscarriage in women with IBD who have not had a previous IBD surgery was based on data from 189 pregnancies (3 studies).

Summary of findings 2. Laparoscopic compared to open surgery for inflammatory bowel disease and female infertility

Risk of infertility among women undergoing surgery with a laparoscopic approach compared to an open approach

Patient or population: females with inflammatory bowel disease

Setting: outpatient

Intervention: laparoscopic surgery

Comparison: open surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with open surgery	Risk with laparoscopic surgery				
Infertility at 12 months	Study population		RR 0.70 (0.38 to 1.27)	19 (1 observational study)	⊕⊕⊕⊕ Very low ^{a,b}	
	647 per 1000	453 per 1000 (246 to 822)				
Infertility at 24 months	These outcomes were not reported					
Miscarriage						
Stillbirth						
Use of ART						
Caesarean section						
Preterm delivery						
Low birth weight						
Small for gestational age						

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ART: assisted reproductive technology; CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded due to high overall risk of bias.

^bDowngraded due to imprecise estimates.

BACKGROUND

Description of the condition

Inflammatory bowel disease (IBD) is an immune-mediated disorder characterized by chronic inflammation of the gastrointestinal tract (Baumgart 2007). The main subtypes of IBD are Crohn's disease (CD), ulcerative colitis (UC), and IBD-type unclassified (IBDU). UC affects the colonic mucosa, and CD can affect any segment of the gastrointestinal tract with transmural inflammation (Baumgart 2007). Patients with IBDU have colonic IBD and present with characteristics of both CD and UC (Silverberg 2005).

IBD is a remitting and relapsing disease (Rahimi 2008). During a period of active disease, affected individuals can experience symptoms of diarrhea, abdominal pain, nausea, malnutrition, and extreme fatigue (Carter 2004). Although genetic, environmental, and microbial factors all play a role in the pathogenesis of IBD, the exact cause of IBD remains to be determined (Loftus 2004).

Treatment options for IBD include pharmacotherapy, such as corticosteroids, immunomodulators, and biologic agents that alter immune function to minimize inflammatory burden (Kozuch 2008). Surgical intervention may be required when patients do not respond to medical therapy (Loewardi 2003). At present, no cure for IBD is known. The goals of both pharmacologic and surgical treatment are to reduce underlying inflammation and maintain remission.

IBD is most commonly diagnosed between the second and fourth decades of life, during a period of peak reproductive potential for females (Benchimol 2014). Infertility does not appear to differ between women without IBD and those with IBD before undergoing surgery (De Felice 2014). However, available surgical treatments may impact infertility. An increase in infertility is described in the literature among women who undergo surgery for UC. Specifically, colectomy with ileal pouch anal anastomosis (IPAA), a procedure that is commonly performed in people with medically refractory UC (Olsen 2002), was noted to increase infertility (Hudson 1997; Rajaratnam 2011; Waljee 2006). However, the degree to which IPAA may affect infertility remains unclear, and whether other surgical interventions for IBD result in measurable changes in infertility is also unclear.

Description of the intervention

Restorative proctocolectomy with IPAA is the standard surgical treatment for UC (Buskens 2014; Koh 2016), and approximately 15% of patients with UC undergo a colectomy within 10 years of diagnosis (Frolkis 2013). IPAA involves the construction of an internal pouch utilizing a distal portion of the remaining small intestine to create a reservoir for stool (McGuire 2007). These surgeries are frequently performed in multiple stages. An ileal pouch can be made and anastomosed to the anus immediately following proctocolectomy (one-stage IPAA). Alternatively, the same ileal pouch can be protected from the fecal stream by a loop ileostomy, which is subsequently reversed in a second procedure (two-stage IPAA). A three-stage option exists as well, in which a total abdominal colectomy and ileostomy are first performed. This is followed by completion proctectomy with an IPAA and loop ileostomy as the second stage, and loop ileostomy reversal as the third stage. The indication for the colectomy (emergent or elective) often influences the choice of procedure.

Nearly 50% of patients with CD will require an intestinal resection within 10 years of diagnosis, and 25% undergo a second resection within five years of their first surgery (Frolkis 2013; Frolkis 2014). Patients with CD may require surgery for medically refractory disease or because of complications, including abscesses, fistulae, strictures, toxic megacolon, or intestinal perforation. Similar to patients with UC, patients with CD may undergo colectomy but typically would not proceed to an IPAA due to the likelihood of disease recurrence in the pouch resulting in pouch dysfunction. In addition, patients may require a small intestinal resection, most often involving removal of a portion of the ileum with primary anastomosis. Alternatively, patients with narrowed intestinal segment(s) resulting from an accumulation of scar tissue may undergo a strictureplasty. In this procedure, a lengthwise incision is made in the narrowed segment of intestine then is sutured together widthwise. The goals of strictureplasty are to preserve length and to minimize the risk of short bowel syndrome. Patients with perianal CD may undergo surgical procedures such as abscess drainage, seton placement, fistulotomy, fistulectomy, or the creation of an ostomy to divert fecal effluent (de Zoeten 2013).

Surgical procedures used in the management of IBD can be performed as conventional open surgeries or as minimally invasive techniques, such as the multiport laparoscopic approach. Open surgeries require a large incision along the abdomen, providing direct access to the small and/or large bowel. In contrast, a multiport laparoscopic procedure requires multiple small incisions made in the abdomen and insertion of specialized instruments into the openings to perform the operation. Compared to the traditional open approach, the laparoscopic procedure is less invasive and decreases overall mortality, reduces risk of ileus, and results in a faster return of bowel function (Gu 2014).

Patients with IBD not requiring surgery are typically prescribed medication that suppresses the immune system, where the goal of treatment is to heal the mucosal lining of the gastrointestinal tract. Available options include systemic and non-systemic steroids, immunomodulators (azathioprine or methotrexate), and biologics (infliximab, adalimumab, certolizumab, golimumab, vedolizumab, and ustekinumab). Methotrexate is contraindicated in pregnancy due to its teratogenic effects on a developing fetus. Our review primarily compares infertility and pregnancy-related outcomes in women undergoing IBD-related surgery versus those with medically managed disease. We compare these same outcomes in women who have had open and laparoscopic procedures.

How the intervention might work

Surgical effects on infertility

Studies have reported increased infertility among women with IBD who have undergone an IPAA, with infertility rates ranging from 44% to 82% (Rajaratnam 2011; Waljee 2006). Surgical interventions may result in infertility due to scarring of the fallopian tubes. More recent research suggests that a laparoscopic approach may result in decreased rates of infertility when compared to open surgery (Bartels 2012; Beyer-Berjot 2013).

Previous systematic reviews and meta-analyses exclusively investigated the effects of IPAA on infertility (Rajaratnam 2011; Waljee 2006). This review provides a systematic evaluation of the effects of multiple surgical treatments for IBD on female infertility for women with both CD and UC. We reviewed colectomy, bowel

resection, strictureplasty, and perianal surgery in patients with CD and UC, as well as the impact of open versus laparoscopic surgical techniques.

Why it is important to do this review

Our review expands the scope of previous systematic reviews on the impact of surgery on infertility in women with IBD (Rajaratnam 2011; Waljee 2006). Specifically, we addressed the complete range of surgeries for women with IBD, including both CD and UC, and the implications these different procedures have for infertility and pregnancy-related outcomes. To adequately counsel women requiring surgical intervention for IBD, it is important to correctly establish the relationship between surgical interventions and risk of infertility. Additionally, knowledge of the effects of surgical techniques on infertility could inform practices and procedures with the goal of preserving fertility and improving outcomes for children born to women who have undergone surgery for IBD. We conducted a systematic review and meta-analysis to establish whether women with IBD who have undergone surgery have greater risk of infertility and to determine the magnitude of the association and the rates of infertility among women undergoing different surgical procedures. We also characterized the outcomes of pregnancy in these women.

OBJECTIVES

Primary objective

- To determine the effects of surgical interventions for IBD on female infertility.

Secondary objectives

- To evaluate the impact of these surgical interventions on the need for assisted reproductive technology (ART), time to pregnancy, risk of miscarriage, risk of stillbirth, risk of prematurity, mode of delivery (spontaneous vaginal, instrumental vaginal, or Caesarean section), infant requirement for resuscitation and/or neonatal intensive care, low and very low birth weight, small for gestational age, antenatal and postpartum hemorrhage, retained placenta, postpartum depression, gestational diabetes, and gestational hypertension/preeclampsia.

METHODS

Criteria for considering studies for this review

Types of studies

Interventional or observational studies (cohort and case-control) of women of reproductive age (12 years and older) who underwent surgery for IBD were included in the review. Eligible studies provided a comparison of infertility and/or secondary outcomes between IBD patients undergoing different types of surgery or between patients with IBD undergoing surgery and those not undergoing surgery (i.e. treated medically). Studies comparing infertility and/or secondary outcomes in patients before and after they underwent surgery were included. We excluded cross-over studies, case series, and case reports.

Types of participants

Studies with females of reproductive age with CD, UC, or IBDU were included. Studies comparing patients with IBD to non-IBD control patients were excluded. In addition, we excluded studies that combined patients with IBD with those undergoing similar surgeries for other indications (e.g. familial adenomatous polyposis).

Types of interventions

For CD, UC, and IBDU, we determined the relative rate of infertility following partial colectomy, total colectomy with or without removal of the rectal stump, and IPAA. In addition, we determined the infertility risk following small bowel resection for CD with or without large bowel resection.

Where possible, we assessed infertility rates through the following comparisons.

- Colectomy (laparoscopic) versus colectomy (open) (CD, UC, IBDU).
- Small bowel resection versus pharmacologic treatment without surgery (CD only).
- Colectomy versus pharmacologic treatment without surgery (CD, UC, IBDU).
- Colectomy with IPAA versus colectomy and ostomy without IPAA (CD, UC, IBDU).
- IPAA (laparoscopic) versus IPAA (open).
- Surgical versus medical management of perianal disease (CD only).
- Any type of intestinal resection versus non-surgical management (CD, UC, IBDU).

Comparisons could reflect the primary objective of the study or a secondary objective. For example, we included studies if they primarily compared women with IBD and those without IBD and secondarily compared women with IBD based on the above comparisons. In addition, we included studies that compared women with IBD before and after any of the above surgical procedures.

Types of outcome measures

Primary outcomes

Primary outcomes included the following:

- Risk of infertility, defined as inability to become pregnant after one year of regular unprotected sexual intercourse without the use of birth control; and
- Infertility after 6 months, 18 months, and 24 months.

Secondary outcomes

Secondary outcomes included the following:

- Risk of miscarriage (spontaneous abortion);
- Risk of stillbirth;
- Use of ART, including hormonal or mechanical treatments and in vitro fertilization;
- Spontaneous vaginal delivery, instrumental vaginal delivery (forceps or vacuum at delivery), delivery by elective Caesarean section, and delivery by emergency Caesarean section;

- Prematurity (categorized as birth at < 28 completed weeks' gestation, at 28 to < 32 completed weeks' gestation, at 32 to < 37 completed weeks' gestation);
- Infant requirement for resuscitation and/or neonatal intensive care;
- Low birth weight (< 2500 g);
- Very low birth weight (< 1500 g);
- Small for gestational age (birth weight below the 10th percentile for gestational age);
- Antenatal hemorrhage;
- Postpartum hemorrhage ($\geq$ 500 mL blood loss following a vaginal birth or $\geq$ 1000 mL blood loss following a Caesarean section);
- Retained placenta;
- Postpartum depression;
- Gestational diabetes;
- Gestational hypertension/preeclampsia;
- Time to pregnancy; and
- Fertility rate (total number of children that would be born to each woman if she were to live to the end of her childbearing years).

All outcomes (primary and secondary), when available, were included in the summary of findings tables.

Search methods for identification of studies

Electronic searches

We searched the following databases from inception to September 27, 2018.

- MEDLINE;
- Embase + Embase Classic;
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library; and
- Cochrane IBD Group Specialized Register.

Searching other resources

Additional articles and trials were identified by:

- reviewing references cited in the published literature (included studies and relevant review articles);
- contacting study investigators to identify any ongoing studies;
- searching published abstracts from conferences (American College of Gastroenterology, Digestive Disease Week, United European Gastroenterology Week) for the past five years;
- conducting a search of the grey literature including the grey literature databases Open System for Information on Grey Literature (OpenSIGLE), European Association for Grey Literature Exploration (EAGLE), and National Technical Information Service (NTIS) ([Higgins 2011](#)); and
- searching the clinical trial registries including ClinicalTrials.gov, the World Health Organization (WHO) Trials Portal, and the European Clinical Trials Register (EU-CTR).

Data collection and analysis

Selection of studies

Two review authors (SL and MC) independently reviewed the titles and abstracts identified by the literature search. For those suspected to meet our inclusion criteria, we conducted a review of the full article to determine eligibility. We resolved disagreements by consensus with a third review author (CHS, EIB, or MEK). We used a PRISMA flowchart to document the process for selection of studies. We included studies published in any language following translation. We used DistillerSR (Evidence Partners, Ottawa, Canada) to facilitate abstract and full-text reviews.

Data extraction and management

We developed a standardized data extraction form using DistillerSR (Evidence Partners, Ottawa, Canada) to electronically record and organize data as they were extracted. Two review authors (SL and MC) independently extracted data from all included studies. Agreement between extractors was determined, and disagreements were resolved by consensus with CHS, EIB, or MEK. We extracted the following data.

- Details of the study including:
 - * year of publication;
 - * journal name;
 - * volume and issue;
 - * lead author; and
 - * full title of study.
- Study methods including:
 - * study design - randomized controlled trial (RCT) or observational study (and type, if applicable);
 - * method used to recruit patients for the study;
 - * randomization, blinding, and allocation concealment method (if RCT); and
 - * inclusion and exclusion criteria.
- Characteristics of women included in the studies such as:
 - * number of women in the study;
 - * age of women at the time of surgery and at the time of the study;
 - * type of IBD: CD (with or without perianal disease), UC, or IBDU;
 - * disease activity and study authors' definition of disease activity, when available; and
 - * concomitant and past medications.
- Details of intervention and comparator arms including:
 - * type of surgery;
 - * number of previous surgeries;
 - * surgical approach used (e.g. open or laparoscopic); and
 - * approach to disease management when the comparator was not surgical.
- Details of infertility and pregnancy-related outcomes for intervention and comparator groups including:
 - * definition of infertility used in the study;
 - * infertility at 6, 12, 18, and 24 months; and
 - * measures of secondary outcomes including miscarriage, stillbirth, prematurity, mode of delivery, infant requirement for resuscitation and/or neonatal intensive care, low birth weight, very low birth weight, small for gestational age,

time to pregnancy, fertility rate, antenatal or postpartum hemorrhage, retained placenta, postpartum depression, gestational diabetes, and gestational hypertension/preeclampsia.

Assessment of risk of bias in included studies

Two review authors (SL and MC) independently assessed the risk of bias of included studies (all observational), using the Newcastle-Ottawa Scale (Wells 2011). These studies were assessed for the following domains: (1) selection of study participants; (2) comparability (of cases and controls for case-control studies, and of exposed and non-exposed for cohort studies); (3) outcome assessment (cohort studies only); and (4) exposure assessment (case-control studies only). A maximum of one star was awarded per domain for the selection, exposure, and outcome domains, and a maximum of two stars was awarded for the comparability domain. Stars are indicative of low risk of bias (denoted with green circles in our summary figure), whereas no stars indicates that studies are at high risk of bias (denoted with red circles in our summary figure). Studies with unclear risk of bias are denoted with yellow circles in our summary figure.

We planned to assess the risk of bias of randomized controlled trials (RCTs) using the Cochrane "Risk of bias" tool. This tool assesses bias across six domains: (1) selection bias: random sequence generation and allocation concealment; (2) performance bias: blinding of participants and study personnel; (3) detection bias: blinding of outcome assessment; (4) attrition bias: incomplete outcome data; (5) reporting bias: selective reporting of study outcomes; and (6) other sources of bias (Higgins 2011). We would have rated each domain as having low, high, or unclear risk of bias.

We contacted study authors if insufficient information was provided in the publication to assess risk of bias. If study authors were unable to provide data and information was insufficient to assess the quality of a specific domain, we described the quality of this domain as unclear.

We utilized the GRADE approach to assess the overall quality of evidence, which we rated as (1) high quality, (2) moderate quality, (3) low quality, or (4) very low quality. Observational studies began with a low quality rating but could be upgraded based upon three potential factors: (1) a large magnitude of effect, (2) a judgment that all plausible confounding reduced a demonstrated effect or suggested a spurious effect when results showed no effect, or (3) a dose response gradient (Higgins 2011). We conducted GRADE analyses by using GRADEpro software.

Measures of treatment effect

We used Review Manager (RevMan) 5.3 (The Cochrane Collaboration) to conduct the analyses. For continuous outcomes, we would have calculated the mean difference (MD) and the corresponding 95% confidence interval (CI). For dichotomous variables, we calculated the risk ratio (RR) with 95% CI to compare outcomes for each comparison, where possible. When individual studies reported odds ratios (ORs) with corresponding CIs that were adjusted for confounding variables and did not provide raw contingency tables, we pooled ORs instead of RRs using the generic inverse variance method.

Unit of analysis issues

Cluster randomized trials

Cluster randomized trials can result in unit of analysis errors. Had we identified cluster randomized trials for inclusion in our study, we would have completed approximate analysis by calculating effective sample sizes for each trial.

Cross-over studies

Studies in which participants undergo multiple interventions may result in unit of analysis issues. Given the permanency of surgical intervention, it was not possible to compare infertility in women undergoing surgery for IBD in the context of a cross-over study. Therefore, we excluded cross-over studies.

Repeated measures

For studies that reported multiple observations of the same patient (e.g. infertility measured before and after surgical intervention), we provided a qualitative synthesis of findings to minimize bias resulting from unmatched analyses (Higgins 2011).

Dealing with missing data

Missing variance

If the variance of effect estimates for relevant outcomes were not reported in identified studies, we calculated the standard deviation from the standard error, confidence intervals, P values, or t values. When this information was not reported, we contacted study authors to request these statistics. If study authors were unable to provide this information, we imputed the variance, using the technique recommended by Wiebe 2006, based on the availability of variance estimates from other studies.

Missing patient data

In cases where outcomes of some study participants were not reported (i.e. participants were lost to follow-up), we contacted study authors to obtain this information. If study authors were unable to provide these data, we carried the most recent observation forward (e.g. if a woman was infertile at 12 months, it was assumed that she was also infertile at 18 months). We conducted a sensitivity analysis to compare the results of using available cases and using imputed values by carrying the last observation forward.

Missing outcome data

If identified studies did not report on all outcomes (primary and secondary), we contacted study authors to obtain these data. When these data were not available, we acknowledged this as a limitation of our study and identified it as an area for future research.

Assessment of heterogeneity

We assessed heterogeneity by (1) visually inspecting forest plots; (2) calculating the Chi² statistic with a P value of 0.10 or less indicating statistically significant heterogeneity; and (3) calculating the I² statistic to assess the magnitude of heterogeneity. We interpreted I² values as follows.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.

- 75% to 100%: considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

We did not construct a funnel plot nor test for funnel plot asymmetry as no analyses included more than ten studies (Higgins 2011).

Data synthesis

We pooled data for analysis if interventions, patient groups, and outcomes were sufficiently similar, as determined by consensus between SL, MC, CHS, EIB, and MEK. We did not pool data if there was a high degree of heterogeneity between studies (i.e. $I^2 > 75\%$). In addition, we did not pool studies if review authors believed there were important clinical or methodological differences across studies. We performed a random-effects meta-analysis to account for expected heterogeneity between studies. We conducted all analyses using RevMan 5.3.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses.

- Type of IBD: CD versus UC versus IBDU.
- Age of women at surgery (< 18 years, 18 to 34 years, ≥ 35 years).

We had additionally planned the following subgroup analyses but could not complete them due to lack of data among the included studies.

- Open versus laparoscopic surgical approach (when applicable).
- Use of adhesion barrier agents.
- Left-sided ulcerative colitis versus extensive colitis versus ulcerative proctitis.
- Stricturing CD versus penetrating CD versus non-stricturing, non-penetrating CD.

Sensitivity analysis

We conducted a sensitivity analysis separately to analyze population-based studies versus studies recruiting patients from

tertiary care centers. We additionally conducted a post-hoc sensitivity analysis excluding pregnancy in women with active disease at conception or a diagnosis of IBD during pregnancy or postpartum. We had planned the following sensitivity analyses but could not complete them as no studies met the criteria and/or studies did not report the required data.

- Excluding all studies with overall high risk of bias.
- Excluding studies published only as an abstract.
- Limiting analysis to randomized studies.
- Limiting analysis to women who had a viable pregnancy before undergoing surgery for management of their IBD.

RESULTS

Description of studies

Results of the search

Through our search of MEDLINE, Embase, and Cochrane CENTRAL, we identified 1092 records, with an additional three records obtained from review of references of included studies and relevant review articles (Figure 1). After duplicates were removed, 829 abstracts remained and underwent review; 151 full texts were assessed for eligibility. Sixteen observational studies were identified and included in the review. We identified no randomized studies. Ten studies included data on our specified comparisons and were synthesized quantitatively (i.e. were included in outcome- and comparison-specific meta-analyses). Seven studies compared the risk of infertility and/or secondary outcomes in women before and after surgery and were summarized qualitatively. One included study provided both a comparison of women with IPAA versus women without previous surgery and a comparison of women with IPAA before and after surgery; this study was included in both the meta-analysis and the qualitative summary. We have described in Table 1 and Table 2, the sample size and outcomes of studies included in the meta-analysis and in the qualitative synthesis.

Figure 1. Study flow diagram.

Figure 1. (Continued)

synthesis
(meta-analysis)

Included studies

Infertility

Meta-analysis

Three studies were included in a meta-analysis evaluating the impact of surgical procedures on female infertility in women with IBD at 12 months; two compared patients with and without prior surgery ([Johnson 2004](#); [Koivusalo 2009](#)), and one compared laparoscopic and open IPAA ([Bartels 2012](#)). One study evaluated infertility at 24 months, comparing patients with and without prior surgery ([Hudson 1997](#)).

Qualitative summary

Five studies comparing female infertility before and after surgery at 12 months ([Gorgun 2004](#); [Johnson 2004](#); [Mortier 2006](#); [Olsen 2002](#); [Tulchinsky 2013](#)), one study comparing infertility before and after surgery at six months ([Mortier 2006](#)), and two studies on infertility at 24 months were summarized qualitatively ([Mortier 2006](#); [Olsen 2002](#)). All studies included patients with UC only.

Pregnancy-related secondary outcomes

Meta-analysis

Eight studies were included in meta-analyses evaluating the association between surgical procedures and the following secondary outcomes ([Banks 1957](#); [Bortoli 2011](#); [Hudson 1997](#); [Johnson 2004](#); [Moser 2000](#); [Naganuma 2011](#); [Nielsen 1984](#); [Zavorova 2017](#)):

- Miscarriage was evaluated in five studies. Three studies included patients with CD ([Bortoli 2011](#); [Hudson 1997](#); [Nielsen 1984](#)), one study included patients with UC ([Banks 1957](#)), and one study grouped patients with all types of IBD ([Naganuma 2011](#)).
- Stillbirth was evaluated in three studies. Two studies included patients with CD ([Hudson 1997](#); [Nielsen 1984](#)), and the third included patients with UC ([Banks 1957](#)).
- Use of ART was evaluated in a single study of patients with UC ([Johnson 2004](#)).
- One study included delivery via Caesarean section as an outcome, reporting findings separately for patients with CD and UC ([Zavorova 2017](#)).
- Preterm birth was an outcome in three studies. Two studies included only patients with CD ([Hudson 1997](#); [Nielsen 1984](#)), and one study included both patients with CD and patients with UC ([Zavorova 2017](#)).
- One study evaluated low birth weight, reporting CD- and UC-specific associations ([Zavorova 2017](#)).
- One study, including only patients with CD, included small for gestational age (≤ 10 th percentile) as an outcome ([Moser 2000](#)).

Qualitative summary

Five studies compared secondary pregnancy-related outcomes before and after surgery ([Gorgun 2004](#); [Hahnloser 2004](#); [Mortier 2006](#); [Ravid 2002](#); [Tulchinsky 2013](#)), and all studies included only women with UC. These studies evaluated the following outcomes:

- Miscarriage ([Hahnloser 2004](#); [Ravid 2002](#); [Tulchinsky 2013](#));
- Stillbirth ([Hahnloser 2004](#); [Ravid 2002](#));
- Use of ART ([Gorgun 2004](#); [Johnson 2004](#); [Tulchinsky 2013](#));
- Caesarean section ([Ravid 2002](#); [Tulchinsky 2013](#));
- Gestational diabetes ([Hahnloser 2004](#));
- Preeclampsia ([Hahnloser 2004](#)); and
- Time to pregnancy ([Mortier 2006](#); [Tulchinsky 2013](#)).

Descriptions of included studies

Banks 1957

This retrospective cohort study compared miscarriage and stillbirth in women with definitive previous and no definitive previous surgery for UC. For this study, medical charts of patients admitted for UC at Beth Israel Hospital in Boston, Massachusetts, USA, between 1931 and 1950 were reviewed. UC was broadly defined as colitis, UC, chronic colitis, superficial colitis, or hemorrhagic colitis. Definite surgery included ileostomy, ileostomy and subtotal colectomy, subtotal colectomy, total colectomy, abdominal-perineal resection, colostomy, colostomy and subtotal colectomy, colostomy and local resection, local resection with end-to-end anastomosis, unconventional procedures, explorations, and abdominal-perineal and ileostomy. Data stratified by type of surgery were not reported. A total of 245 patients with UC were included in the study, with one (0.03%) lost to follow-up. Patients with obvious irritable colon syndrome or with inadequate data to support a diagnosis of non-specific UC and ileocolitis were excluded ($n = 13$). Data were collected via personal interviews, patients' physician notes, and hospital records and through correspondence with internists or surgeons. Average patient follow-up was 12.1 years; 73% were followed for ≥ 11 years after disease onset. Data on miscarriage and stillbirth were available for 56 women with 87 pregnancies. Among women included in this study, 28 women with 46 pregnancies were in remission at the time of conception, 14 women with 23 pregnancies had active disease at the time of conception, five women were diagnosed during pregnancy, four women were diagnosed in the postpartum period, and five women (nine pregnancies) had previous surgery. Subsequent pregnancies occurring among women diagnosed during pregnancy or in the postpartum period were excluded due to lack of detailed information about the outcomes of these pregnancies. One pregnancy occurring among women in remission and eight pregnancies among women with active disease at conception ended in therapeutic abortion; no therapeutic abortions were reported among women diagnosed with UC during pregnancy or in the postpartum period. Among 51 women without previous surgery (78 pregnancies), three (3.8%) pregnancies resulted in miscarriage. Among 46 pregnancies in 28 women with inactive disease at conception and no prior surgery for UC, there were two (4.3%) miscarriages. Of the remaining 43 pregnancies, two (4.5%) resulted in stillbirth. Five women (nine pregnancies) underwent prior surgery for UC; two (22.2%) had miscarriages and none had a stillbirth (0%).

Bartels 2012

This cross-sectional study compared the risk of infertility in women with IPAA by a laparoscopic approach versus women with IPAA by an open approach. IPAA was conducted in a single-stage or two-stage procedure with and without the creation of loop ileostomy, with ovaries left unimpaired. Two-stage IPAA consisted of subtotal colectomy followed by complete proctectomy and creation of IPAA. This study was conducted at three university hospitals in The Netherlands and Belgium between February 2010 and February 2011 and included women who underwent IPAA between 1993 and 2009. These patients were identified from hospital databases. Of 179 patients who were eligible for the study, five (2.8%) refused consent and 14 (7.8%) did not respond. An additional 110 patients (61.5%) were excluded because they did not wish to have a child after IPAA. The study included 50 female patients ≥ 18 years of age at the time of the study who had IPAA before 41 years of age (open: $n = 23$; laparoscopic: $n = 27$). Indications for IPAA surgery included UC ($n = 37$), familial adenomatous polyposis ($n = 12$), and others ($n = 1$). Subgroup analyses specific to women with UC were described (open: $n = 20$; laparoscopic: $n = 17$). Data were collected via a self-reported questionnaire that was developed and mailed out to patients, with a reminder sent after three weeks. The questionnaire included questions on medical history, desire for children, infertility, obstetric history before and after IPAA, smoking at the time of conception attempts, history of pelvic inflammatory disease, and history of extrauterine gravidity. Patients with incomplete or unclear answers were contacted. Answers were then verified by a check of available medical records. Average follow-up was 9.4 years (standard deviation [SD] = 5.0 years). Infertility was defined as not becoming pregnant within 12 months of trying to conceive. Infertility at 12 months was reported in nine (45%) women whose surgery was performed via a laparoscopic approach and in 11 (65%) women whose surgery was performed through an open approach.

Bortoli 2011

This prospective cohort study compared women with previous surgery for IBD versus those with no previous surgery for IBD. The surgeries these women underwent were not described. This study was conducted at 68 centers in 12 European countries between 2003 and 2006. The primary objective of this study was to compare women with IBD to those without IBD. Women with IBD who did and did not have prior surgery were also compared. Of 520 pregnant women with IBD enrolled consecutively (CD: $n = 244$; UC: $n = 264$; IBDU: $n = 12$), 332 were matched to non-IBD pregnant controls (CD: $n = 145$; UC: $n = 187$). Women with IBD were excluded if they could not be matched to a woman without IBD ($n = 147$), if their matched control had missing data ($n = 32$), or if they were diagnosed with IBDU ($n = 9$). Each participating center received electronic case report forms for trained physicians to record the requested data prospectively at enrollment and every three months until the end of pregnancy. Information was collected by in-person or telephone interview and by review of patients' medical records. All completed forms were sent electronically to the central database storage. Requested data included maternal variables, treatment for IBD, disease activity, pregnancy outcomes, and mode of delivery. The association between prior surgery and miscarriage was provided only for women with CD. Study authors also described the association between previous surgery and Caesarean section and preterm delivery (< 37 weeks' gestation) in women with CD and the association between previous surgery and Caesarean section in women with UC. However, we did

not include these outcomes, as all pregnancies (including those ending in spontaneous and therapeutic abortion) were included as the denominator, and the true association between surgery and these outcomes could not be ascertained. As a result, we included only women with CD in our meta-analysis. There were 47 (32.4%) pregnant women with CD who had a previous IBD-related surgery, and there was no association between miscarriage and previous surgery among women with CD (OR 1.30, 95% CI 0.21 to 7.90).

Gorgun 2004

This cross-sectional study compared infertility and use of ART before and after restorative proctocolectomy with IPAA in women with UC and familial adenomatous polyposis. Eligible study participants were identified from a prospectively maintained pelvic pouch database from a single center between 1983 and 2001. Of 500 women undergoing pelvic pouch operation between 15 and 44 years of age and eligible for the study, 300 (60.0%) responded to the mailed questionnaire. Of the 300 respondents, 206 (68.7%) attempted to conceive before and/or after restorative proctocolectomy with IPAA (before: $n = 127$; after: $n = 135$; before and after: $n = 56$). The study included 185 women with UC. Of these women, 117 attempted to conceive before surgery and 120 after surgery; 52 attempted to conceive both before and after pregnancy. Female patients self-reported information on infertility before and/or after surgery. Additional information was obtained from the pelvic pouch database, including patients' demographic and disease history and technical characteristics of the surgery. Infertility was defined as 12 months of unprotected intercourse without conception among women trying to conceive. There were 45 (38.5%) women with UC who were infertile before restorative proctocolectomy with IPAA and 70 (58.3%) women with UC who were infertile after restorative proctocolectomy with IPAA. In a subgroup analysis of women trying to conceive both before and after restorative proctocolectomy, 24 of 52 (46.2%) were infertile before restorative proctocolectomy with IPAA and 36/52 (69.2%) were infertile afterward. Of 45 women who were infertile before restorative proctocolectomy with IPAA, 19 (42.2%) women used ART, whereas 36 of 70 (51.4%) women who were infertile after restorative proctocolectomy used ART.

Hahnloser 2004

This cross-sectional study compared outcomes of pregnancy in women before and after IPAA. IPAA involved either excising the anal transition zone and hand-sewing the pouch to the anal canal or preserving the anal transition zone and double-stapling the pouch of the anal canal. All patients had a diverting ileostomy constructed, which was closed two to three months after IPAA construction. Eligible patients were identified from a prospectively maintained database of all individuals undergoing IPAA between 1981 and 1995. A total of 544 female patients underwent IPAA for UC before 40 years of age and underwent colectomy, complete mobilization of the small bowel mesentery, and proximal rectal mobilization via a close rectal dissection technique. All eligible patients identified in a prospective hospital database as having undergone IPAA for UC were sent a standardized questionnaire, which included information on pregnancy outcomes and mode of delivery before and after IPAA. The response rate was 82.7% (450/544), and the mean follow-up after IPAA was 13 years. Outcomes included miscarriage, stillbirth, gestational diabetes, and preeclampsia. Of the 450 respondents, 141 were pregnant

(236 pregnancies) after diagnosis with UC but before IPAA and 135 (30.0%) were pregnant (232 pregnancies) after IPAA. Eight (1.8%) women were excluded from the analyses because the time of pregnancy was not reported. Data on outcomes of pregnancy occurring before IPAA were reported with the number of women as the denominator, and the number of pregnancies was the denominator for outcomes of pregnancies occurring after IPAA. Of the 141 women who were pregnant before IPAA, 27 (19.1%) had a miscarriage, four (2.8%) had a stillbirth, 16 (11.3%) had preeclampsia, and 14 (10.6%) had gestational diabetes. Of the 232 pregnancies occurring after IPAA, 31 (14.4%) were miscarriages and two (0.9%) were stillbirths. Information on complications of pregnancy was missing for 16 of 232 pregnancies occurring after IPAA. Of the 216 pregnancies with data on complications, mothers developed gestational diabetes in five (2.3%) and preeclampsia in ten (4.6%). A total of 52 women were pregnant before and after IPAA, of whom 37 (71.2%) had data available for both time periods. Data are included for the first pregnancy following IPAA. Before IPAA, ten women (27.0%) had a miscarriage, two (5.4%) had a stillbirth, three (8.1%) had gestational diabetes, and two (5.4%) had preeclampsia. Of the same 37 female patients with UC who were pregnant after IPAA, six (16.2%) had a miscarriage, two (5.4%) had a stillbirth, and no women had gestational diabetes or preeclampsia. This study also reported information on mode of delivery; however, these results were not presented as miscarriages, and stillbirths were combined with the denominator for mode of delivery, resulting in biased estimates of the impact of surgery on the need for Caesarean section.

Hudson 1997

This cross-sectional study compared infertility and pregnancy-related outcomes in women with IBD with and without prior surgical intervention. Detailed information about the type(s) of surgical procedures and the approach to medical management was not provided. This study was conducted at one large teaching hospital (i.e. a single referral center for gastroenterology, obstetrics, and pathology) in the North East of Scotland, including the Orkney and Shetland Isles, with a stable population of 600,000 over the course of the study. Between 1967 and 1986, 466 women between 16 and 45 years of age had an established diagnosis of CD or UC, based on accepted clinical, radiologic, endoscopic, and/or histologic criteria, who resided in the Grampian Region for six months or longer before the onset of symptoms. A four-page anonymous questionnaire was sent with a prepaid return envelope to eligible women, which included information on menstruation, past and current contraceptive status, desire for pregnancy, date of each delivery, pregnancy outcomes, and any conception difficulty. Additional information was obtained through hospital, medical, or obstetric records and, if necessary, from general practitioners. Of 466 eligible women with CD or UC, 409 (87.8%; CD = 177, UC = 232) responded to the questionnaire. Infertility was defined as failing to achieve a desired spontaneous conception after 24 months of unprotected intercourse. Study authors also included data on miscarriage (spontaneous abortion), stillbirth, and premature delivery among women with CD. No information on pregnancy-related outcomes among women with UC was presented. Of 261 (63.8%; CD n = 123, UC n = 138) women who responded and were potentially fertile, involuntary infertility was analyzed in 86 (69.9%) women with CD and 104 (75.4%) women with UC. The remaining women were voluntarily infertile. Of those with CD, 46 (53.5%) underwent previous surgical intervention and 40 (46.5%)

had disease that was managed only medically. Among women with UC, 11 (10.6%) had prior surgery and UC was managed medically in the remaining 93 (89.4%) women attempting to conceive. Infertility at 24 months was observed in 7 of 46 (15.2%) females with CD who had prior surgery, 3 of 40 (7.5%) females with medically managed CD, 5 of 11 (45.5%) females with UC who had prior surgery, and 8 of 93 (8.6%) females with medically managed UC. A total of 132 pregnancies were observed among women with CD; 79 of these pregnancies occurred in women whose disease was managed medically and 53 pregnancies occurred in women with previous IBD-related surgery. Evidence of recurrent disease based on endoscopy and/or radiology was noted at the time of conception in 14 (26.4%) pregnancies among women with previous surgery. Of the 39 cases that occurred after surgical intervention without objective evidence of disease recurrence, nine (23.1%) resulted in a miscarriage (spontaneous abortion) compared to 9 of 79 (23.1%) women with CD whose disease had been managed only medically and 5 of 14 (36%) with previous surgery and evidence of disease recurrence. Nine therapeutic abortions were reported among women with no previous surgery, four therapeutic abortions among those with past surgery but without evidence of disease recurrence, and two therapeutic abortions among those with previous surgery and recurrent disease. Among the remaining pregnancies, one stillbirth was observed. This occurred in a woman with previous IBD surgery and evidence of recurrent disease. Among pregnancies not ending in miscarriage or therapeutic abortion (n = 94), premature delivery was observed in 2 of 61 (3.3%) pregnancies among women without previous IBD surgery, 1 of 26 (3.8%) pregnancies among women with previous IBD surgery without disease recurrence, and one of seven (14.3%) pregnancies in women with previous surgery and recurrent CD.

Johnson 2004

This cross-sectional study compared the risk of infertility and the need for ART among women with UC who had an IPAA versus medically managed UC. Eligible patients were identified from a prospectively maintained IBD database at Mount Sinai Hospital, in Toronto, Canada. Details of IPAA and the approach to medical management in these patients were not described. There were 560 female patients with UC who were registered in the IBD database (IPAA: n = 323; medical treatment: n = 237). Information in the IBD database at Mount Sinai Hospital was prospectively collected and entered. Identified female patients were sent questionnaires by mail and were called, to encourage a reply or to clarify any missing data. A total of 397 (70.9%) women completed and returned the questionnaire, including 254 with IPAA and 143 with medically managed disease. A total of 213 (IPAA: n = 153; medical treatment: n = 60) women met the eligibility criteria: ≥ 18 years of age at time of study, < 44 years of age at time of IPAA or diagnosis of UC, and married or cohabitating for at least 12 months after surgery or after diagnosis. Patients with incomplete data regarding relationship history and reproductive history were excluded. The mean (SD) duration of follow-up after IPAA was 11.6 (4) years, and the mean (SD) duration of follow-up after diagnosis for women with medically managed UC was 15.6 (10.7) years. Infertility was defined as failure to become pregnant during 12 months of unprotected intercourse. Among the 153 women with an IPAA included in the study, 95 attempted to become pregnant before surgery and 66 attempted to become pregnant after surgery. Among women with an IPAA, infertility was observed in 4 of 95 (4.2%) before surgery and in 29 of 66 (43.9%) after surgery. Among the 40 women who did not have

surgery, 1 of 40 (2.5%) was infertile. ART was used in 5 of 95 (5.3%) women who would later have an IPAA, 20 of 66 (30.3%) women after undergoing IPAA, and 0 of 40 (0%) women without prior surgery for UC.

Koivusalo 2009

This cross-sectional study compared infertility among women with UC who underwent restorative proctocolectomy with IPAA and those without prior surgery. Women in the group with restorative proctocolectomy with ileoanal anastomosis had J-pouch or straight ileoanal anastomosis. Indications for surgery were UC recalcitrant to medical treatment and fulminant colitis. In the group receiving medical management, patients were on 5-ASA and azathioprine, 5-ASA, mercaptopurine, prednisone, or no medication. This study included patients treated at two major university hospitals (i.e. Helsinki and Tampere) in Finland between 1985 and 2005. Data were collected by self-reported questionnaire during a follow-up outpatient visit. The questionnaire collected information on sexual function, bowel function, stool frequency, fecal incontinence, and medication use. Out of 81 eligible patients with prior surgery, 79 (97.5%) were traced and invited for a follow-up outpatient visit and 36 (45.6%) attended. This included 25 (69.4%; 17 female) with pediatric-onset UC (diagnosed < 16 years of age) who underwent restorative proctocolectomy with ileoanal anastomosis, were sexually active, and were > 16 years of age at the time of the study. These patients were compared to 38 (19 female) controls who were sexually active, were medically treated for UC, and were > 16 years of age at the time of the study. Infertility was defined as not becoming pregnant within 12 months after trying to conceive. Among 17 women who underwent restorative proctocolectomy with ileoanal anastomosis, five (29.4%) attempted pregnancy and infertility was observed in three (60.0%) women. Among 19 women who were medically treated for UC, three attempted pregnancy, and infertility was observed in one of three (33.3%) women.

Mortier 2006

This cross-sectional study compared infertility in women with UC before and after total colectomy with ileorectal anastomosis. Details of the surgical procedure were not provided. Data were collected between May and September 2003. Eligible patients were treated at a single center (Department of Abdominal Surgery, Centre Hospitalier Régional Universitaire de Lille, in Lille, France) between 1962 and 1999. Data were collected via structured interviews conducted via telephone by instructed and trained female interviewers. The same set of questions was asked to gather information about three time periods: before diagnosis of UC, from diagnosis of UC to ileorectal anastomosis, and from ileorectal anastomosis to the date of the interview. No patient was lost to follow-up, and the median follow-up was 16 years (range 4 to 35 years). A total of 37 female patients underwent ileorectal anastomosis for UC. Patients were excluded if they died from postoperative complications or alcoholic cirrhosis (n = 2), had a confirmed diagnosis of CD (n = 5), or underwent proctectomy for rectal cancer (n = 1). Infertility was defined as the proportion of those not pregnant with unprotected intercourse at 6, 12, and 24 months. Five (13.5%) women desired to become pregnant before surgery, and 15 (40.5%) women attempted pregnancy afterward. Infertility at six months was observed in one of five (20.0%) females before colectomy with ileorectal anastomosis and in 9 of 15 (60.0%) females afterward. Infertility at 12 months was observed in one

of five (20.0%) females before total colectomy with ileorectal anastomosis and in 8 of 15 (53.3%) females after total colectomy with ileorectal anastomosis. Infertility at 24 months was observed in one of five (20.0%) women before surgery and in 7 of 15 (46.7%) women afterward. Before surgery, the median (range) time to pregnancy was two (one to three) months compared to five (2 to 36) months after surgery.

Moser 2000

This retrospective cohort study evaluated the risk of having a baby that was small for gestational age among women with CD who did and did not have a prior bowel resection. The details of surgical intervention were not provided. Patients whose medical charts included a code for pregnancy and IBD or CD between January 1993 and December 1997 were examined for eligibility. This study was conducted in Edmonton, Canada. Retrospective chart reviews were conducted by reviewing the data on prenatal sheets, the discharge data summary, and the neonate's history and physical examination findings. Women were eligible for the study if there was documentation in their charts of pregnancy and IBD, CD, or gastrointestinal consultation (n = 91). Patients were excluded if they were admitted for missed therapeutic abortion, abortion, or spontaneous abortion before 20 weeks (n = 23) or had active disease at the time of conception (n = 5). The study included 65 women with CD whose pregnancy had gone beyond 32 weeks (76 pregnancies). Only one pregnancy was selected at random for women with multiple pregnancies in the study period. Thus, 65 women with CD with 65 pregnancies were matched to healthy controls selected by a computer from the Northern Alberta Perinatal Outreach Program database by age, parity, smoking status, approximate date of delivery, and gestational age. The primary objective of this study was to compare women with CD versus healthy controls. However, study authors assessed predictors of giving birth to an infant who was small for gestational age, defined as < 10th percentile, among women with CD. Of 65 included pregnancies, 41 (63.1%) occurred after previous bowel resection and 24 (36.9%) pregnancies occurred in women with no previous bowel resection. Infants were small for gestational age in 13 (31.7%) and three (12.5%) pregnancies that occurred in women with and without previous bowel resection, respectively. With adjustments for smoking during pregnancy, ileal disease location, and poor weight gain (< 15 pounds throughout pregnancy or < 10 pounds by the 28th week of gestation), the OR (95% CI) for the association was 4.16 (0.92 to 18.92).

Naganuma 2011

This cross-sectional study compared several pregnancy-related outcomes in women with and without previous surgery for IBD. Details of the surgical procedures these women underwent were not provided. Study participants were women with IBD treated at six large IBD centers in Japan who conceived between 1989 and 2008. A questionnaire was given to participants that collected information on type of disease, marital status, number of children, smoking habits, age at each conception, history of surgery for IBD, history of surgery for perianal lesions, abscesses and fissuring ulcerations in CD patients, history of therapy for infertility, outcomes of conceptions, mode of delivery, birth weight, and presence of congenital abnormalities. Female patients, when pregnant, were given a notebook to report information regarding conception and outcomes of pregnancy. Information on the course of pregnancy and its outcomes (including birth

weight) was completed by physicians or nurses. Medical records were reviewed to confirm the diagnosis of disease, continuation or discontinuation of medications at the time of conception, outcomes, mode of delivery, and congenital malformation. Of 589 patients enrolled in the study, 11 (1.9%) refused to participate and six (1.0%) patients with indeterminate colitis were excluded. In total, there were 325 female patients (CD: $n = 80$; UC: $n = 245$) between the ages of 17 and 46 years who experienced conception at least once and were eligible to participate in the study. A total of 534 conceptions were reported among women participating in the study, of which 303 (CD: $n = 69$; UC: $n = 234$) occurred during or after IBD onset. Miscarriage, Caesarean section, and low birth weight were included as outcomes. However, we included only miscarriage data, as the true association between previous surgery and other outcomes could not be determined because study authors included pregnancies ending in spontaneous and therapeutic abortion among those at risk. Among 303 conceptions occurring during or after IBD onset, 60 (19.8%; CD: $n = 44$; UC: $n = 16$) occurred in women with previous surgery. CD and UC were combined for all analyses reported in this paper. Previous surgery was not associated with miscarriage in pregnant women with IBD (OR 1.4, 95% CI 0.71 to 2.90).

Nielsen 1984

This retrospective cohort study evaluated the association between pregnancy outcomes in women with CD who did and did not have a previous intestinal resection. Details of the surgical intervention were not provided. This study included patients treated in outpatient clinics or admitted to hospital at a single center in Copenhagen, Denmark, between January 1968 and December 1980. Information was obtained through a review of medical records, and women with insufficient data were contacted by telephone. Participants included 68 women (149 pregnancies) with CD under the age of 37 years at the time of conception. Of 149 pregnancies, 40 (36.7%) occurred before the beginning of the study period or ended six months before the onset of disease and were excluded. Of 68 women, 51 (75.0%) had previous bowel resection. These 51 women had a total of 77 pregnancies, and 17 women without prior surgery had 32 pregnancies. Of the 109 pregnancies, 57 occurred among women with quiescent disease at conception, 43 occurred among women with active disease at conception, three occurred among women who were diagnosed during pregnancy, and six occurred in women who were diagnosed postpartum. Based on the information provided, we were not able to exclude patients with active disease at conception. Eleven and eight therapeutic abortions were reported among women with and without previous surgery, respectively. With exclusion of pregnancies ending in miscarriage or therapeutic abortion, three (5.3%) pregnancies in women with previous bowel resection resulted in stillbirth compared to one (4.3%) pregnancy in women without prior surgery. There were 13 (22.8%) pregnancies resulting in preterm birth among women with previous surgery compared to two (8.7%) in women with no prior bowel resection. Nine (11.7%) miscarriages and one (3.1%) miscarriage occurred in women with and without prior surgery, respectively.

Olsen 2002

This cross-sectional study compared infertility before and after restorative proctocolectomy with IPAA. Details of the surgical procedure were not provided. Eligible patients were treated at four centers in Denmark and Sweden between November 1982

and January 1998; they were contacted by letter to obtain consent or refusal. Non-responders whose telephone numbers could be found in the directory were contacted by telephone. Data were collected by telephone interview via a highly structured interview form conducted thoroughly by trained female interviewers. Information about the following time periods was collected during the interview: before the diagnosis of UC, from diagnosis until colectomy, and from stoma closure until the date of the interview (after IPAA). Participants were asked once about reproductive history, starting and ending dates, duration of the first interval of unprotected intercourse in each time window, intent to become pregnant or pregnancy planning, and exposures around the starting date of this first-time interval. Study participants were 343 women with UC who underwent restorative proctocolectomy with IPAA; they were ≤ 40 years old at the time of stoma closure and > 18 years of age at the time of the interview. Of 343 women with UC who were eligible for the study, 290 (84.5%) agreed to participate and provided information. These women had a total of 331 attempted pregnancies (before diagnosis: $n = 98$, before colectomy: $n = 84$, after IPAA: $n = 149$). Infertility was defined as the inverse of the probability of becoming pregnant within 12 and 24 months of unprotected intercourse. Infertility at 12 months was observed in 18 of 84 (21.4%) attempted pregnancies before colectomy and in 122 of 149 (81.9%) attempted pregnancies after IPAA. Infertility at 24 months was observed in 13 of 84 (15.5%) attempted pregnancies before surgery and in 108 of 149 (72.5%) attempted pregnancies after surgery.

Ravid 2002

This cross-sectional study compared infertility and outcomes of pregnancy (miscarriage and Caesarean section) before and after IPAA. A total of 26 female patients had a stapled J-pouch and 12 female patients had an S-pouch. In all, 18 female patients had a three-stage operation, 18 female patients had a two-stage operation, and two female patients had a one-stage operation. Seventeen had a hand-sewn ileoanal anastomosis, and the anastomosis was stapled in 21. There were nine patients without loop ileostomy. Eligible patients underwent IPAA at the Inflammatory Bowel Disease Unit of Mount Sinai Hospital, in Toronto, Ontario, Canada, between 1982 and 1998. Questionnaires were sent to eligible patients to collect information on infertility, pregnancy, type of delivery, birth weight of the baby, and complications of pregnancy and pouch. Female patients who had become pregnant after IPAA construction and gave birth at least once after IPAA were further contacted by telephone. Pouch function before, during, and after pregnancy was assessed with questions related to stool frequency, incontinence during the day and night, pad usage, skin irritation, and medication usage. Of a total of 1088 IPAAs performed, 481 (44.2%) female patients were identified and 400 (83.2%) female patients responded to the questionnaire, including 38 (9.5%) who became pregnant a total of 67 times after IPAA. At the time of the study, 2 of the 67 pregnancies occurring after IPAA were ongoing; these pregnancies were excluded from the analysis. Of the 38 women who gave birth after IPAA, 12 (31.6%) had also given birth before IPAA (16 pregnancies). One of 16 (6.3%) pregnancies resulted in a miscarriage before IPAA, and 9 of 65 (13.8%) pregnancies resulted in a miscarriage after IPAA. Four therapeutic abortions were performed before IPAA and seven therapeutic abortions after IPAA. Before IPAA, none of the remaining 11 pregnancies resulted in a stillbirth or were delivered by Caesarean section. After IPAA, one

of the 49 (2.0%) remaining pregnancies resulted in a stillbirth; 24 of 49 (49.0%) were delivered by Caesarean section.

Tulchinsky 2013

This cross-sectional cohort study compared infertility, use of ART, time to pregnancy, and pregnancy-related outcomes before and after restorative proctocolectomy. Details of the surgical interventions were not provided. Study participants were identified from a prospectively collected database of patients from a comprehensive pouch clinic at a tertiary referral center in Israel. Participants were contacted during visits to the clinic or by telephone. Eligible participants filled out a questionnaire on infertility, pregnancy, delivery, newborn status, issues on time to conceive, need for infertility therapies, medical treatment before and during pregnancy, miscarriages, duration of pregnancy, and pregnancy-related complications. Additional information, such as patient demographics, past medical history, and history of operations, was collected from the pouch clinic database and during patient visits. Among 55 women with UC who underwent restorative proctocolectomy before the age of 45 and who were ≥ 21 years of age at the time of the study, 47 (85.5%) met the inclusion criteria and 41 (87.2%) returned the questionnaire. Before surgery, 26 women had 70 pregnancies. Following restorative proctocolectomy, 27 women attempted pregnancy; 32 pregnancies were reported among 17 women. Infertility was defined as the inability to achieve conception after one year of unprotected sex with a fertile male partner. None of the 26 women were infertile before surgery, and 10 of 27 (37.0%) were infertile afterward. Among 11 women attempting pregnancy both before and after surgery, none were infertile before surgery, and six (54.5%) were infertile after surgery. Eight of 70 (11.4%) pregnancies resulted in a miscarriage before surgery compared to 6 of 32 (18.8%) pregnancies after surgery. A total of 6 of 70 (8.6%) pregnancies used ART before restorative proctocolectomy and 11 of 32 (34.4%) afterward. Eight of 62 (12.9%) pregnancies were delivered by Caesarean section before restorative proctocolectomy compared to 12 of 26 (46.2%) delivered by Caesarean section after restorative proctocolectomy. The mean (SD) time to pregnancy was 5.0 (11.6) months before surgery and 16.3 (25.1) months afterward.

Zavorova 2017

This retrospective cohort study compared pregnancy-related outcomes in women with and without previous surgery for IBD. Surgery for women with UC included IPAA. Surgery for women with CD included a mix of colectomy with end ileostomy, ileocecal resection with anastomosis, and other procedures. Medical treatment in 10 female patients with CD included mesalazine ($n = 2$), a combination of mesalazine and budesonide ($n = 1$), azathioprine ($n = 3$), azathioprine and adalimumab ($n = 1$), infliximab ($n = 1$), and adalimumab ($n = 2$). This study was conducted in the Department of Obstetrics and Gynecology at the Hospital Horovice in the Czech Republic, between October 2014 and March 2016. Data on infertility, therapy during pregnancy, and mode of delivery were obtained from the hospital database. Loss

to follow-up was not reported. Participants included 17 female patients (CD: $n = 12$; UC: $n = 5$). Seven women with CD who had no prior surgery gave birth nine times. Of these infants, two (22.2%) were born by Caesarean section, one (11.1%) had low birth weight, and none were born prematurely (< 37 weeks' gestation). Five women with previous surgery for CD delivered five babies, four of whom were delivered by Caesarean section. None of the infants born to women with CD who had prior surgery were low birth weight or were born prematurely. The birth weight of one infant born to a mother with CD who had previous surgery was missing. Three women with UC with no previous surgery had four deliveries, and two women with UC who had prior IPAA delivered two babies. Half (2/4) of the deliveries in women with UC without IPAA and both (2/2) of the deliveries in women with UC and an IPAA were performed via Caesarean section. One (25.0%) low birth weight baby was born and one (25.0%) infant was born prematurely to a mother without prior surgery for UC, compared to no low birth weight or premature births among women with UC who had an IPAA.

Excluded studies

Of the 151 studies identified for full-text review, 135 were excluded (see [Characteristics of excluded studies](#)). Excluded studies were review articles and studies that did not include infertility or one of our secondary outcomes, were not limited to women with IBD, and did not include an eligible comparison group ([Figure 1](#)).

Risk of bias in included studies

The risk of bias in the 16 included observational studies is summarized in [Figure 2](#). Overall, we found high risk of selection bias in terms of the representativeness of the exposed cohort and selection of the non-exposed cohort, comparability of cohorts, and outcome assessment. Only one study was at low risk of selection bias based on the representativeness of the cohort and selection of the non-exposed cohort ([Hudson 1997](#)); the risk of bias due to selection of exposed and non-exposed individuals was unclear in one study ([Hahnloser 2004](#)). Three studies were at high risk of bias based on methods used to ascertain surgical status ([Bortoli 2011](#); [Hudson 1997](#); [Olsen 2002](#)), and the method used to determine surgical status was unclear in two studies ([Johnson 2004](#); [Koivusalo 2009](#)). The outcome of interest was not present at the start of each study, resulting in low risk of selection bias for this domain. Only three studies presented adjusted analyses and were at low risk of bias for this domain ([Bortoli 2011](#); [Moser 2000](#); [Naganuma 2011](#)). In five studies ([Bartels 2012](#); [Moser 2000](#); [Naganuma 2011](#); [Nielsen 1984](#); [Zavorova 2017](#)), outcomes were obtained from medical records or from an existing database; therefore, these studies were at low risk of bias for outcome assessment. The remaining studies were at high risk of bias because outcomes were ascertained from patient self-report. Generally, follow-up was long enough for outcomes to occur, but risk of bias due to length of follow-up was unclear in two studies ([Koivusalo 2009](#); [Zavorova 2017](#)). Four studies had high risk of bias due to poor response rates ([Gorgun 2004](#); [Johnson 2004](#); [Koivusalo 2009](#); [Olsen 2002](#)), and the risk of bias for this domain was unclear in one study ([Zavorova 2017](#)).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Representativeness of cohort (selection bias)	Selection of the non-exposed cohort (selection bias)	Ascertainment of exposure (selection bias)	Outcome of interest was not present at start of study (selection bias)	Comparability of cohorts on the basis of the design or analysis (comparability)	Assessment of outcome (outcome)	Was follow-up long enough for outcomes to occur (outcome)	Adequacy of follow up cohorts (outcome)
Banks 1957	+	+	+	+	+	+	+	+
Bartels 2012	+	+	+	+	+	+	+	+
Bortoli 2011	+	+	+	+	+	+	+	+
Gorgun 2004	+	+	+	+	+	+	+	+
Hahnloser 2004	?	?	+	+	+	+	+	+
Hudson 1997	+	+	+	+	+	+	+	+
Johnson 2004	+	+	?	+	+	+	+	+
Koivusalo 2009	+	+	?	+	+	+	?	+
Mortier 2006	+	+	+	+	+	+	+	+
Moser 2000	+	+	+	+	+	+	+	+
Naganuma 2011	+	+	+	+	+	+	+	+
Nielsen 1984	+	+	+	+	+	+	+	+
Olsen 2002	+	+	+	+	+	+	+	+
Ravid 2002	+	+	+	+	+	+	+	+
Tulchinsky 2013	+	+	+	+	+	+	+	+
Zavorova 2017	+	+	+	+	+	+	?	?

Figure 2. (Continued)

Effects of interventions

See: [Summary of findings for the main comparison](#) Any previous surgery compared to no previous surgery for inflammatory bowel disease on female infertility; [Summary of findings 2](#) Laparoscopic compared to open surgery for inflammatory bowel disease and female infertility

Any previous surgery vs no previous surgery

Infertility at 12 months

Two studies compared the risk of infertility at 12 months in women with UC who did and did not have previous surgery (see [Analysis 1.1](#); [Johnson 2004](#); [Koivusalo 2009](#)) (RR 5.45, 95% CI 0.41 to 72.57; 114 participants). Heterogeneity between studies was substantial ($I^2 = 74\%$). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates. [Johnson 2004](#) compared women with previous IPAA to those with no previous surgery, and [Koivusalo 2009](#) compared women with restorative proctocolectomy with ileoanal anastomosis to those with no previous surgery.

Infertility at 24 months

The risk of infertility at 24 months among women with and without previous surgery for IBD was compared in a single study, which reported findings separately for CD and UC (see [Analysis 1.2](#); [Hudson 1997](#)). The following associations between previous surgery and 24-month infertility were observed:

- CD: RR 2.03, 95% CI 0.56 to 7.33, 86 participants;
- UC: RR 5.28, 95% CI 2.09 to 13.34, 104 participants; and
- Combining women with CD and UC: RR 3.59, 95% CI 1.32 to 9.73, 190 participants.

There was no notable heterogeneity ($I^2 = 39\%$). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates. [Hudson 1997](#) compared women with and without previous IBD-related surgery but provided no specific details on the types of surgical procedures performed.

Miscarriage

Five studies compared the association between previous surgery for IBD and miscarriage (see [Analysis 1.3](#); [Banks 1957](#); [Bortoli 2011](#); [Hudson 1997](#); [Naganuma 2011](#); [Nielsen 1984](#)) (OR 2.03, 95% CI 1.14 to 3.60; 776 pregnancies; $I^2 = 0\%$). Three studies evaluated this association among pregnancies in women with CD (OR 2.56, 95% CI 1.19 to 5.51; 386 pregnancies), and one study evaluated this association among pregnancies in women with UC (OR 7.14, 95% CI 1.02 to 50.18; 87 pregnancies). Findings were similar in a single population-based study (OR 2.79, 95% CI 1.11 to 7.04; 132 pregnancies) and in four studies recruiting patients from tertiary care centers (OR 1.84, 95% CI 0.84 to 4.03; 644 pregnancies) (see [Analysis 1.4](#)). Results were also similar in a sensitivity analysis of two studies excluding patients with active disease at the time of conception (RR 2.38, 95% CI 1.11 to 5.11; 173 pregnancies; $I^2 =$

0%) (see [Analysis 1.5](#); [Banks 1957](#); [Hudson 1997](#)). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias. All studies compared women with and without previous IBD-related surgery, and none provided detailed information on the types of surgical procedures the women required.

Stillbirth

Three studies evaluated the association between previous surgery and stillbirth in women with IBD (RR 1.96, 95% CI 0.42 to 9.18; 246 pregnancies; $I^2 = 0\%$), two evaluating the risk in women with CD (RR 1.98, 95% CI 0.32 to 12.16; 174 pregnancies; $I^2 = 0\%$) and the other in women with UC (RR 1.91, 95% CI 0.10 to 36.02; 72 pregnancies; $I^2 = 0\%$) (see [Analysis 1.6](#); [Hudson 1997](#); [Nielsen 1984](#); [Banks 1957](#)). One study was population based ([Hudson 1997](#)), and the other two included women treated at tertiary care centers ([Banks 1957](#); [Nielsen 1984](#)), reporting the following results (see [Analysis 1.7](#)):

- Population-based: RR 5.47, 95% CI 0.23 to 130.65; 94 pregnancies; and
- Tertiary care: RR 1.43, 95% CI 0.24 to 8.35; 152 pregnancies; $I^2 = 0\%$.

Two studies were included in a sensitivity analysis excluding pregnancies in women with active disease at conception (see [Analysis 1.8](#); [Banks 1957](#); [Hudson 1997](#)). No stillbirths were reported in [Hudson 1997](#) among women in remission at conception, so no estimate of the association between previous surgery and stillbirth could be obtained from this study. In [Banks 1957](#), the association between previous surgery and stillbirth in women with inactive UC at conception was RR 1.26 (95% CI 0.07 to 23.54; 72 pregnancies). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates. Studies compared women with and without previous IBD-related surgery but provided no specific details on the types of surgical procedures the women required.

Use of ART

The association between previous surgery and use of ART was evaluated in a single study of 106 women with UC (see [Analysis 1.9](#)): RR 25.09, 95% CI 1.56 to 403.76 ([Johnson 2004](#)). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates.

Caesarean section

The association between previous surgery and delivery via Caesarean section among women with IBD was reported in a single study, with stratification by type of IBD (see [Analysis 1.10](#); [Zavorova 2017](#)):

- CD: RR 3.60, 95% CI 0.98 to 13.19; 14 pregnancies;
- UC: RR 1.67, 95% CI 0.61 to 4.59; 6 pregnancies; and
- Combining CD and UC: RR 2.23, 95% CI 1.00 to 4.95; 20 pregnancies; $I^2 = 0\%$.

Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias. All women with UC in [Zavorova 2017](#) requiring surgery had IPAA and were compared to those without previous surgery; the women with CD underwent a variety of procedures.

Prematurity

Three studies determined the association between preterm birth among women with and without previous surgery (RR 1.91, 95% CI 0.67 to 5.48; 194 pregnancies; $I^2 = 0\%$) (see [Analysis 1.11](#); [Hudson 1997](#); [Nielsen 1984](#); [Zavorova 2017](#)). All three studies evaluated this association in women with CD (RR 2.32, 95% CI 0.75 to 7.21; 188 pregnancies; $I^2 = 0\%$), and one study also evaluated this association in women with UC (RR 0.56, 95% CI 0.03 to 9.73; 6 pregnancies). Findings were similar in a single population-based study (RR 1.85, 95% CI 0.27 to 12.53; 94 pregnancies) and in two studies recruiting patients from tertiary care centers (RR 2.02, 95% CI 0.56 to 7.28; 100 pregnancies) (see [Analysis 1.12](#)). One study was included in a sensitivity analysis limited to women in remission at the time of conception (RR 1.17, 95% CI 0.11 to 12.38; 87 pregnancies) (see [Analysis 1.13](#); [Hudson 1997](#)). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates. [Bortoli 2011](#), [Hudson 1997](#), and [Nielsen 1984](#) all compared women with and without previous IBD-related surgery without providing specific details of the surgical procedures. All women with UC in [Zavorova 2017](#) requiring surgery had IPAA and were compared to those without previous surgery; the women with CD had a variety of surgical procedures.

Low birth weight

The association between previous IBD surgery and giving birth to a low birth weight infant was evaluated in a single study ([Zavorova 2017](#)), which reported the association in women with CD (RR 0.67, 95% CI 0.03 to 13.60; 13 pregnancies) and UC (RR 0.56, 95% CI 0.03 to 9.73; 6 pregnancies). When CD was combined with UC, this association was RR 0.61 (95% CI 0.08 to 4.83; 19 pregnancies) (see [Analysis 1.14](#)). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates. All women with UC requiring surgery had IPAA and were compared to those without previous surgery; the women with CD underwent a variety of procedures.

Very low birth weight

One study allowed for the association between surgery and giving birth to a very low birth weight baby ([Zavorova 2017](#)). Of 14 pregnancies in women with CD and six pregnancies in women with UC, none resulted in the birth of a very low birth weight infant.

Small for gestational age

The association between previous surgery and giving birth to a small for gestational age infant was evaluated in a single study that included only women with CD: RR 2.54, 95% CI 0.80 to 8.01; 65 pregnancies (see [Analysis 1.15](#); [Moser 2000](#)). The association was similar when adjusting for poor weight gain during pregnancy, ileal disease location, and tobacco use during pregnancy (OR 4.16, 95% CI 0.92 to 18.92). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very

low due to high overall risk of bias and imprecise estimates. No details were provided about the types of surgery women required.

Laparoscopic vs open surgery

Infertility at 12 months

One study compared a laparoscopic approach and an open approach to restorative proctocolectomy with regard to female infertility at 12 months in 37 women with UC: RR 0.70, 95% CI 0.38 to 1.27 (see [Analysis 2.1](#); [Bartels 2012](#)). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias and imprecise estimates.

Before and after surgery

Infertility at 12 months

Five studies assessed infertility at 12 months before and after surgery (see [Table 3](#); [Gorgun 2004](#); [Johnson 2004](#); [Mortier 2006](#); [Olsen 2002](#); [Tulchinsky 2013](#)). All studies were limited to women with UC. Surgeries included restorative proctocolectomy with IPAA, restorative proctocolectomy, and total colectomy with ileorectal anastomosis. Before surgery, 68 of 327 (20.8%) females reported that they were infertile following 12 months of unprotected intercourse. Following surgery, 239 of 377 (63.4%) females were infertile after 12 months. [Gorgun 2004](#) additionally reported on a subgroup of 52 women with UC who attempted pregnancy both before and after IPAA; 24 of 52 (46.2%) women were infertile before surgery and 36 of 52 (69.2%) were infertile after surgery. This study also reported infertility before and after surgery stratified by age at surgery. Age-specific findings are summarized in [Table 4](#). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Infertility at six months

One study assessed infertility at six months before and after colectomy with ileorectal anastomosis ([Mortier 2006](#)). Among five women with attempted pregnancy before surgery, one (20.0%) was infertile. Infertility was reported by 9 of 15 (60%) of women attempting pregnancy after surgery. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Infertility at 24 months

Two studies observed infertility at 24 months before and after surgery in female patients with UC (see [Table 5](#); [Mortier 2006](#); [Olsen 2002](#)). Overall, 14 of 89 (15.7%) females with UC were infertile before surgery and 116 of 164 (70.7%) were infertile after surgery. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias. Surgeries included restorative proctocolectomy with IPAA and total colectomy with ileorectal anastomosis.

Miscarriage

Three studies observed miscarriage before and after surgery in females with UC (see [Table 6](#); [Hahnloser 2004](#); [Ravid 2002](#); [Tulchinsky 2013](#)). There were 19 of 123 (15.4%) and 21 of 134 (15.7%) pregnancies before and after surgery, respectively, that resulted in miscarriage. Based on GRADE analyses, the overall

certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Stillbirth

Two studies examined stillbirth in women with UC before and after IPAA (see [Table 7](#); [Hahnloser 2004](#); [Ravid 2002](#)). Before surgery, 2 of 38 (5.3%) resulted in a stillbirth compared to 3 of 80 (3.8%) pregnancies occurring after surgery. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Use of ART

Three studies observed use of ART before and after surgery in female patients with UC (see [Table 8](#); [Gorgun 2004](#); [Johnson 2004](#); [Tulchinsky 2013](#)). Due to differences in the denominator for each study, results are not combined. [Gorgun 2004](#) reported that 19 of 45 (42.2%) women who were infertile at 12 months used ART before restorative proctocolectomy with IPAA and 36 of 70 (51.4%) used ART after surgery. [Johnson 2004](#) reported the proportion of women using ART among all women attempting pregnancy, finding that 5 of 95 (5.3%) used ART before IPAA compared with 20 of 66 (30.3%) after IPAA. [Tulchinsky 2013](#) reported that ART was used in 6 of 70 (8.6%) pregnancies occurring before restorative proctocolectomy compared with 11 of 32 (34.3%) pregnancies after surgery. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Caesarean section

Two studies described delivery by Caesarean section before and after surgery in females with UC ([Ravid 2002](#); [Tulchinsky 2013](#)). Eight of 73 (11.0%) deliveries occurred by Caesarean section before surgery and 36 of 75 (48.0%) deliveries occurred by Caesarean section after surgery (see [Table 9](#)). Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias. Surgeries included IPAA and restorative proctocolectomy.

Gestational diabetes

One study observed gestational diabetes before and after surgery in female patients with UC ([Hahnloser 2004](#)). Among the 37 women with pregnancies before and after IPAA, three (8.1%) women developed gestational diabetes before surgery and no women experienced gestational diabetes in a pregnancy after surgery. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Preeclampsia

One study observed preeclampsia before and after IPAA among women with UC ([Hahnloser 2004](#)). Of the 37 women with pregnancies before and after IPAA, two (5.4%) had preeclampsia before surgery compared to 0 after surgery. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

Time to pregnancy

Two studies observed time to pregnancy before and after surgery among women with UC (see [Table 10](#); [Mortier 2006](#); [Tulchinsky 2013](#)). [Mortier 2006](#) reported that the median (range)

time to pregnancy among five women attempting pregnancy before colectomy with ileorectal anastomosis was two months (one to three) compared to five months (2 to 36) among 15 women attempting pregnancy after surgery. [Tulchinsky 2013](#) reported that the mean (SD) time to pregnancy before restorative proctocolectomy was 5.0 (11.6) months among 26 women attempting pregnancy, with conception reported as occurring "immediately" in 32 pregnancies. Among 27 women attempting to conceive after surgery, the mean (SD) time to conception was 16.3 (25.1) months. Based on GRADE analyses, the overall certainty of evidence was downgraded from low (observational study) to very low due to high overall risk of bias.

DISCUSSION

Summary of main results

Based on available data, we are uncertain about the association between previous IBD-related surgery and risk of infertility in women with IBD due to very low-quality evidence. Data on the association between previous surgery and infertility at 12 months were limited to women with UC, while data on infertility at 24 months were available for both CD and UC. It is uncertain if there are any differences in infertility among women with UC who underwent surgery via a laparoscopic or open approach. Further, although no associations were observed between IBD-related surgery and risk of stillbirth, preterm delivery, or delivery of a low birth weight or small for gestational age infant, and associations were observed with miscarriage, use of ART, and Caesarean section delivery, the evidence supporting these associations is uncertain. Our conclusions are based on very low-quality evidence due to the observational nature of the data, the limited number of studies, the small sample sizes of the studies, and high risk of bias. Thus, our findings should be interpreted with caution.

Overall completeness and applicability of evidence

We lacked data on several of the comparisons and outcomes we sought to investigate. Specifically, we were able to present data only from studies comparing colectomies conducted via open and laparoscopic approaches and from studies comparing women who had previous surgery versus those who did not. Although some studies defined the types of surgical procedures that women underwent, no two studies evaluating infertility and providing specific details of the type of surgical procedure included women who had the same surgical procedure. We additionally reported data on studies comparing infertility and pregnancy-related outcomes in women before and after colectomy and/or IPAA. However, as outlined below, we are concerned about the validity of these studies. We had initially aimed to describe the impact of specific surgeries (i.e. IPAA, small bowel resection, perianal surgery) on infertility and secondary outcomes, but many of the included studies grouped multiple surgery types into a single comparison and did not provide any details of the type(s) of surgery the women included in their studies required. Given that variation across types of surgery is likely, the applicability of our findings for women considering an IBD-related intestinal resection is limited. For example, the creation of an IPAA is a pelvic surgery that is more likely to result in damage to the fallopian tubes when compared with more limited intestinal resections (e.g. small bowel resection) ([Asztély 1991](#); [Oresland 1994](#)). Tubal factors were found to be a more common reason for infertility among women with an IPAA compared to women without an IPAA and may be

less likely to result from other procedures (Pabby 2015). Further, variations may exist across types of pouches and techniques used for their construction. Some studies included women with J, S, or Kock pouches. One small study reported a numeric increase in adhesions among women who underwent three-stage IPAA construction compared to women who had a two-stage procedure, which may subsequently impact the risk of infertility (Hull 2012). Another study reported numeric increases in infertility among those with a stapled anastomosis compared to those with a hand-sewn anastomosis (Harnoy 2016).

In addition to missing data on several specific comparisons, we did not identify any studies evaluating several of our specified secondary outcomes, including requirement for instrumental delivery, infant resuscitation, antenatal hemorrhage, postpartum hemorrhage, retained placenta, postpartum depression, and fertility rate. Thus, we are unable to draw conclusions with regard to how these pregnancy outcomes may be impacted by previous IBD-related surgery.

Quality of the evidence

All studies were identified as having high risk of bias for at least one domain. All but one of the included studies recruited patients from tertiary care centers and were at risk of selection bias (Hudson 1997). For example, at smaller hospitals, less experienced surgeons may perform surgery in patients with IBD, which may result in higher infertility rates. Alternatively, patients treated at tertiary care centers may have more severe or more complicated disease, resulting in more complicated surgery. However, results of sensitivity analyses (when possible) demonstrated that results were similar in population-based studies and in studies recruiting patients from tertiary care centers. Further, most studies did not adjust for important confounding factors. Several studies relied on self-reported data for outcome assessment and/or exposure ascertainment. The use of self-reported data could result in reporting biases, whereby women with previous IBD-related surgery may be more likely to recall having trouble becoming pregnant or experiencing a negative outcome of pregnancy. Additionally, these women may be more likely to notice an early miscarriage compared to women without prior surgery. Most studies included participants for a sufficient length of time for outcomes to develop, and studies had high response and retention rates.

The presence of selection bias and lack of control for important confounding factors (e.g. maternal age, disease activity or severity, corticosteroid use, presence of perianal disease) prevented us from drawing conclusions about the impact of surgery on infertility and pregnancy outcomes in women with IBD. Specifically, active IBD and corticosteroid use during pregnancy are associated with negative outcomes, including giving birth to a premature or low birth weight infant and miscarriage, and methotrexate is teratogenic (Boyd 2015; Bröms 2014; Mahadevan 2007; Mahadevan 2017; Nguyen 2016). Although some studies presented adjusted results, one study was limited to patients in remission at conception and adjusted for ileal disease location (Moser 2000). Two additional studies presented data stratified by disease activity at conception, enabling a sensitivity analysis of pregnancies occurring among women in remission at conception. None of the studies evaluating infertility accounted for maternal age. Fertility declines with age and failure to account for maternal age particularly impacts studies

comparing infertility in women before and after undergoing surgery (Crawford 2015). Additionally, delivery via Caesarean section is contraindicated in women with active perianal disease (Nguyen 2016); thus, findings may have been confounded by disease phenotype. Further, studies did not provide information on the time between surgery and attempts at pregnancy, which may also have confounded the associations investigated in this review. Last, several studies included multiple pregnancies per mother. Thus, information on several pregnancy outcomes may be biased on the basis that women who are more likely to achieve and sustain a healthy pregnancy are likely over represented. Further, the precision of the estimate is biased by failing to account for clustering of data within mothers (Vittinghoff 2005).

In addition to several concerns about the risk of bias among individual studies, we are concerned that our findings are exclusively drawn from observational studies. However, a randomized controlled clinical trial could not be ethically implemented to evaluate this research question. Further, most analyses were based on five or fewer studies, and these studies had small sample sizes, resulting in imprecise estimates. Additionally, we noted high heterogeneity for some comparisons. As a result of high risk of bias among included studies, as well as high levels of imprecision, all conclusions made in this review are based on very low-quality evidence and, as such, should be interpreted with caution.

Potential biases in the review process

We systematically reviewed several databases, conference abstracts, and references of identified review articles and included studies to identify all studies comparing the risk of infertility and several pregnancy-related outcomes in women with IBD who did and did not have previous IBD-related surgery. All screening of abstracts, reviews of full texts, and data extraction were done in duplicate by two independent review authors. Thus, bias in identifying studies was minimized. However, bias may have resulted from incomplete outcome reporting. For example, we were unable to identify relevant studies for several of our outcomes. Further, some outcomes were included in the identified studies, but these studies provided insufficient information to allow for inclusion in the systematic review. Last, we may have introduced bias through our calculation of the absolute risk of some secondary outcomes. Specifically, for studies reporting only an adjusted odds ratio and corresponding confidence intervals, numerator and denominator data used to calculate the absolute risk for each intervention arm were not available. Instead, these data were calculated from the data available in studies included in the review that provided contingency tables for relevant associations.

Agreements and disagreements with other studies or reviews

Infertility

Two previous systematic reviews specifically evaluated the impact of IPAA on infertility. One was limited to patients with UC (Waljee 2006), and the other included patients with UC and familial adenomatous polyposis (Rajaratnam 2011). Both concluded that infertility occurred more often in women with an IPAA compared to women without an IPAA. Our review differed from these previous reviews in that we included only studies that used a rigorous definition of infertility (i.e. an inability to become pregnant

within a specified length of time such as 12 months of regular unprotected sexual intercourse without the use of birth control). This was an important distinction, as not using such a definition may result in biased conclusions, particularly if women without previous IBD-related surgery are followed longer than patients with previous IBD-related surgery. For example, if two women received the diagnosis of IBD at 23 years of age (one without surgery and one with surgery at 26 years of age) and were followed until age 30, the woman without previous surgery would have seven years of follow-up data, whereas the woman with previous surgery would have only four years of follow-up data. With longer follow-up, the first woman is more likely to conceive, regardless of previous surgery. Consequently, lower infertility rates among patients without previous surgery may result from a longer period during which to conceive. Further, women with IBD who undergo surgery may be systematically different from those who do not undergo surgery. They may have more severe disease, long-term disability, or systemic effects of chronic inflammation or steroid use. Therefore, they may be less likely to want to become pregnant, resulting in perceived higher infertility rates.

Another difference from other systematic reviews is that we did not meta-analyze studies assessing infertility in women before and after IPAA construction. These studies were not pooled due to concerns about the statistical validity of failing to account for repeated observations in the analysis, as well as the clinical factors that may affect women's choice to become pregnant, as described above. Studies comparing infertility before and after IPAA construction were biased due to confounding by age. Specifically, women were older in the postoperative period, which may have also contributed to postoperative infertility. Age-specific estimates of infertility before and after IPAA were reported in one study (Gorgun 2004). No differences in infertility were reported among women undergoing surgery before the age of 30, and rates of infertility were higher following IPAA after the age of 30 - an age after which fertility begins to decline more rapidly than at previous ages (Crawford 2015), likely biasing study authors' overall findings.

Because of our decision not to pool studies comparing infertility before and after surgery, we were not able to meta-analyze any studies evaluating the impact of IPAA on infertility. Although studies included in our qualitative summary did report an increased proportion of women being infertile following IPAA and ileorectal anastomosis procedures (Gorgun 2004; Mortier 2006; Olsen 2002), we are unable to make any statistical inferences about the impact of IPAA on infertility in women with IBD given the concerns with available data described above.

Definition of infertility

We specifically defined infertility as an inability to become pregnant after 12 months of unprotected intercourse and included additional time points (i.e. 6, 18, and 24 months) as secondary outcomes. Thus, we included only studies that reported the proportion of women who were infertile among those who were attempting to become pregnant. Other studies have used alternative definitions of infertility (e.g. live births, success of in vitro fertilization) or have included women who were married or cohabitating, regardless of whether or not they were trying to conceive. Although our definition of infertility was aimed at estimating the risk of infertility among women attempting to conceive, some studies excluded from this review have taken a broader approach to defining

infertility, grouping voluntary infertility (i.e. choosing not to get pregnant) with involuntary infertility. That is, these studies have mixed women who choose not to become pregnant for disease-related or other reasons with those who are unable to become pregnant despite trying to conceive. Both approaches may lead to biased conclusions with regard to the impact of IBD surgeries on female infertility. Further, estimates of infertility can vary drastically across definitions, and the choice of definition can lead to different conclusions when infertility is compared across groups of women (Jacobson 2017).

A prior systematic review identified rates of voluntary infertility among women with IBD ranging from 17% to 38% (Purewal 2018). In a survey of women of childbearing age from the United Kingdom, women who were voluntarily childless had more prior surgeries than women who had children following their IBD diagnosis (Selinger 2016). Voluntary childlessness among women with IBD is related to poorer pregnancy-related IBD knowledge, as well as anxiety with regard to the heritability of IBD, the ability to raise a child, and the impact of pregnancy on IBD disease activity. It is unclear whether voluntary childlessness in women with IBD, particularly those with prior surgery, results from disease- and surgery-related factors, lack of knowledge, or other psychosocial factors.

Sexual dysfunction may also contribute to infertility among women with IBD. Prior studies have suggested that 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 study findings have not been consistent (Eluri 2018; Sanders 2016). Thus, this 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.

Comparison to other medical conditions

A single study suggests that IPAA increases infertility in women with familial adenomatous polyposis (Olsen 2003). However, this study also compared women before and after surgery and is consequently subject to the same residual confounding resulting from increased age in the postoperative period that resulted in bias in some research involving women with IBD.

Two other studies evaluated the impact of IPAA on infertility by comparing women with IBD who had undergone the surgical procedure to women without IBD who underwent appendectomy. One study was limited to patients with ulcerative colitis and noted higher rates of infertility among women with an IPAA compared to those who underwent appendectomy (Lepisto 2007). The other study included women with IBD and women with familial adenomatous polyposis and found no difference in infertility among the two groups of women (Beyer-Berjot 2013). However, small sample sizes and choice of study design (e.g. definition of infertility) may have resulted in biased results. Notably, Lepisto 2007 defined infertility at 24 months using the same definition that we required for inclusion in our study, and Beyer-Berjot 2013 did not define infertility within a specific time frame. Further, it is unclear if the reduction in infertility observed in these studies was the result of IPAA or IBD, as infertility is more common among women with IBD than in the general population (Tavernier 2013).

Mode of delivery

Based on very low-quality evidence, our review suggests that women with prior IBD-related surgery may be more likely to give birth via Caesarean section compared to women for whom IBD had been managed medically. However, insufficient information is presented among the included studies to determine if this association reflects physician and patient preference or obstetric indications for Caesarean section. Among the studies describing mode of delivery, three studies described reasons for Caesarean section (Hahnloser 2004; Ravid 2002; Zavorova 2017). In Zavorova 2017, Caesarean sections were planned for all women with surgically managed IBD (both CD and UC), whereas Caesarean section was performed only in the presence of obstetric complications among women who had not previously had IBD surgery. In the other two studies, less than a quarter of all deliveries were performed via Caesarean section specifically because the mother had an IPAA, with remaining Caesarean sections occurring for obstetric reasons or because of patient preference (Hahnloser 2004; Ravid 2002). Insufficient information was provided in studies to determine if active perianal disease contributed to decisions with regard to mode of delivery among included studies. A survey of Canadian gastroenterologists reported very little consensus regarding the impact of mode of delivery among women with an IPAA (Kuenzig 2018). More recent clinical practice guidelines indicate that Caesarean section should be recommended for women with IPAA due to concerns about pouch function and sphincter injury after delivery (Nguyen 2016), but this recommendation is based on limited data. Women with active perianal disease are also recommended to deliver via Caesarean section. For all other women with IBD, regardless of surgical history, vaginal delivery is recommended unless there are obstetric indications for Caesarean section (Nguyen 2016). Increasing evidence points to the safety of vaginal delivery for these women, despite earlier concerns about vaginal delivery increasing the risk of or worsening perianal disease (Foulon 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Limited information is available 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 delivery, and giving birth to a low birth weight baby), these observations 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) that may contribute to these outcomes. Thus, we are not able to draw firm conclusions with regard to the impact of IBD-related surgery on female infertility or pregnancy-related outcomes. Although women should be counseled that the risk of infertility after intra-abdominal surgery may be elevated, healthcare providers should caution women that the existing research is of poor quality and limited quantity.

Implications for research

Data on the association between IBD-related surgery and infertility are unclear. IBD-related surgery may alter the risk of some adverse pregnancy outcomes (miscarriage, use of ART, Caesarean section delivery, and giving birth to a low weight baby) while not impacting other outcomes. However, we encountered several

limitations to the included studies. Further, we were not able to include studies evaluating all identified comparisons or outcomes. Thus, well-designed studies are needed to evaluate the impact of surgical procedures on the risk of infertility among women with IBD. Future studies should be large cohort studies in which data on IBD disease activity and phenotype, medical and surgical treatment, and pregnancy attempts and outcomes are collected prospectively. These studies should specifically take the following into consideration:

- Type of surgical procedure. Although some studies allowed specific comparisons across types of procedures, most included studies were limited to comparisons of any intestinal resection relative to no prior intestinal resection. The impact of each procedure (e.g. limited small bowel resection, colectomy with IPAA, colectomy with permanent ileostomy) should be evaluated independently. Further, studies should provide sufficient detail of the surgical procedures to ensure the generalizability of study findings (e.g. open vs laparoscopic, two-stage vs three-stage procedures, hand-sewn vs stapled anastomoses).
- Outcome definitions. Studies varied with regard to how infertility was defined, and the definition of infertility was not always clear. Future studies should use a well-presented and consistent definition to improve the comparability of studies. Further, the contribution of sexual dysfunction to involuntary infertility should be identified to better estimate the impact of surgery on infertility.
- Disease activity, phenotype, and medical treatment. It is well established that active disease results in negative pregnancy-related outcomes. Thus, confounding due to disease activity and phenotype (e.g. disease location, disease behavior, presence of perianal disease, corticosteroid or methotrexate use), as well as previous medication utilization, should be incorporated into the analysis of studies evaluating the impact of surgical procedures on infertility and pregnancy-related outcomes.
- Appropriate comparison groups and statistical analysis. Although studies comparing infertility in women before and after surgery eliminate bias due to between-person differences, additional biases are introduced, such as increasing age of participants and changes in disease activity and phenotype over time. Thus, these factors should be accounted for in the statistical analyses. Further, studies that compare these outcomes in women before and after surgery should use statistical methods that account for the paired nature of the data.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Banks 1957

Methods	<p>STUDY DESIGN: This was a retrospective cohort study conducted at a single center in Boston, Massachusetts, USA, between 1931 and 1950</p> <p>DATA COLLECTION: Retrospective chart review of clinical records for patients admitted to the Beth Israel Hospital was conducted to identify women eligible for the study. Previous surgery status and outcomes were obtained from personal interviews, patients' physicians' clinical notes, and records at hospitals along with correspondence with internists or surgeons</p>
Participants	<p>Participants included 245 patients diagnosed with nonspecific UC (i.e. colitis, UC, chronic colitis, superficial colitis, and hemorrhagic colitis) identified from 702 patient records. Patients with obvious irritable colon syndrome or with inadequate data to support a diagnosis of non-specific ulcerative colitis and ileocolitis were excluded (n = 13). Of 56 women with 87 pregnancies coinciding with UC diagnosis, 14 women with active disease at conception had 23 pregnancies, 5 women with previous surgery had 9 pregnancies, 5 women were diagnosed with UC during pregnancy, and 4 women were diagnosed during the postpartum period</p>
Interventions	<p>The intervention of interest was definitive surgery for ulcerative colitis and no surgery for UC. Definitive surgery for UC included ileostomy, ileostomy and subtotal colectomy, subtotal colectomy, total colectomy, abdominal-perineal resection, colostomy, colostomy and subtotal colectomy, colostomy and local resection, local resection with end-to-end anastomosis, unconventional procedures, explorations, and abdominal-perineal and ileostomy</p>
Outcomes	<p>SECONDARY OUTCOMES: Miscarriage, stillbirth</p>

Banks 1957 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort of female patients who received definitive surgical treatment for colitis were identified from medical records from Beth Israel Hospital in Boston, Massachusetts, USA. This study was identified as having high risk of bias because participants were identified from a tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort of female patients who did not receive a definitive surgical treatment for colitis were identified from the same medical records from Beth Israel Hospital in Boston, Massachusetts, USA. This study was identified as having high risk of bias because participants were identified from a tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained through medical chart review
Outcome of interest was not present at start of study (selection bias)	Low risk	Pregnancy status was determined during the study and researchers asked about pregnancy outcomes
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Information on pregnancy outcomes was based on medical chart review and personal interviews with patients. This study was identified as having high risk because some outcome data were obtained from self-report
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Average follow-up of patients' living was 12.1 years, with 73% followed over more than 11 years from onset of their disease
Adequacy of follow up cohorts (outcome)	Low risk	1/245 (0.03%) were lost to follow-up

Bartels 2012

Methods	<p>STUDY DESIGN: This was a cross-sectional study conducted in 3 university hospitals in the Netherlands and Belgium between February 2010 and February 2011. Women who had undergone IPAA between 1993 and 2009 were identified from hospital databases</p> <p>DATA COLLECTION: A self-reported questionnaire was mailed out to eligible patients with a 3-week reminder. Details of how patients were identified to participate in the study were not provided. Patients with incomplete or unclear survey responses were contacted, and information was clarified. Answers were then verified by checking available medical records. The questionnaire included questions on medical history, desire for children, infertility, obstetric history before and after IPAA, smoking at the time of conception attempt, history of pelvic inflammatory disease, and history of extrauterine gravidity</p>
Participants	Participants included 50 female patients ≥ 18 years of age at the time of the study who had undergone IPAA before 41 years of age. Indications for IPAA included familial adenomatous polyposis, UC, and oth-

Bartels 2012 (Continued)

ers. Subgroup analyses limited to 37 women with UC were presented, including 17 women who underwent open IPAA and 20 who underwent laparoscopic IPAA

Interventions	The intervention of interest was open vs laparoscopic IPAA. Surgery was conducted as a single- or two-stage procedure. Single-stage IPAA was conducted in a single surgical procedure. Two-stage IPAA consisted of subtotal colectomy then complete proctectomy with creation of IPAA. Both were conducted with and without the creation of loop ileostomy with ovaries left unimpaired
Outcomes	PRIMARY OUTCOME: Infertility was defined as not becoming pregnant within 12 months of trying to conceive
Notes	This consisted of patients with mixed medical conditions. There were 37 patients with UC. Subgroup analysis of women with UC was presented

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of all female patients with UC (≥ 18 years) who underwent laparoscopic IPAA before 41 years of age in the 3 university hospitals in Netherlands and in Belgium. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of all females with UC (≥ 18 years) who underwent open IPAA before 41 years of age from the same 3 university hospitals in Netherlands and in Belgium. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Ascertainment of exposure (selection bias)	Low risk	IPAA surgery was searched in the hospital databases
Outcome of interest was not present at start of study (selection bias)	Low risk	Females were selected based on surgical status, then provided information on infertility
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	Low risk	Self-reported questionnaires were distributed and then were verified or completed by a check of available medical records
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Mean (SD) follow-up was 9.4 (5.0) years
Adequacy of follow up cohorts (outcome)	Low risk	A total of 179 patients were eligible for the study; 5 refused consent; 14 did not respond; 110 did not wish to have a child after IPAA. The response rate was 89.4%

Bortoli 2011

Methods	STUDY DESIGN: This was a prospective cohort* study conducted in 12 European countries (total of 68 participating centers) between January 2003 and December 2006 DATA COLLECTION: Each participating center received electronic case report forms on which trained physicians could record the requested data prospectively at study entry and then every 3 months until
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The impact of surgical therapies for inflammatory bowel disease on female fertility (Review)

Bortoli 2011 (Continued)

the end of pregnancy. Information was collected by regular personal or telephone interviews and by review of patients' medical records. All completed forms were sent electronically to the central database storage. Requested data included (1) maternal variables, (2) treatment for IBD, (3) disease activity, (4) outcome of pregnancy, and (5) mode of delivery

Participants	Women with CD or UC were matched with pregnant non-IBD women and non-pregnant IBD women (1:1:1) as the primary objective of this study was to compare women with and without IBD. Matching criteria included age at conception and number of previous pregnancies. A total of 520 pregnant women with IBD were enrolled (CD: 244; UC:264; indeterminate colitis: 12). Only 332 (CD:154; UC: 187) pregnant women with IBD were included in the study (147 women did not match to non-IBD pregnant women, 32 women had missing data, 12 women with indeterminate colitis were excluded). All consecutive pregnancies were included
Interventions	Previous surgery compared to no previous surgery. A detailed description of the types of surgical procedure(s) women with IBD required was not provided
Outcomes	SECONDARY OUTCOMES: Miscarriage (spontaneous abortion), preterm delivery (< 37 weeks' gestation), Caesarean section
Notes	<p>Only the P value for the association between several secondary outcomes and previous surgery was reported for women with UC. Details were insufficient to determine the proportion of women experiencing each outcome among those with previous IBD surgery and those without previous surgery</p> <p>*The study authors described this study as a prospective case-control study. However, the study compared multiple pregnancy-related outcomes in women with and without IBD and should therefore be described as a cohort study</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort included female patients with IBD recruited consecutively who had attempted pregnancy and had previous intestinal surgery from 68 tertiary care centers. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort comprised consecutively recruited female patients with IBD who had attempted pregnancy and did not have previous intestinal surgery (i.e. pharmacologic treatment), recruited from the same tertiary care centers as the exposed cohort. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Ascertainment of exposure (selection bias)	High risk	Review of patients' medical records and personal or telephone interviews. This study was identified as having high risk of bias because some exposure data were obtained from self-report
Outcome of interest was not present at start of study (selection bias)	Low risk	Females were pregnant at the beginning of the study and then were followed for secondary outcomes (i.e. adverse pregnancy outcomes)
Comparability of cohorts on the basis of the design or analysis (comparability)	Low risk	Adjusted for age at conception, smoking, alcohol use
Assessment of outcome (outcome)	High risk	Patients' medical records and personal or telephone interviews were reviewed. This study was identified as having high risk because some outcome data were obtained from self-report

Bortoli 2011 (Continued)

Was follow-up long enough for outcomes to occur (outcome)	Low risk	Female patients with IBD were followed until the end of pregnancy
Adequacy of follow up cohorts (outcome)	Low risk	520 female patients with IBD enrolled. Only 373 were matched to non-IBD pregnant controls (required for the primary objective of the study); 32 (8.6%) female patients with IBD were excluded due to missing data, and no description of the missing data was provided

Gorgun 2004

Methods	<p>STUDY DESIGN: This was a cross-sectional study conducted using patients identified from a pelvic pouch database that captures information on patients seen at a single center in Cleveland, Ohio, USA, between 1983 and 2001</p> <p>DATA COLLECTION: Participants were mailed a consent form and questionnaire regarding infertility before and after operation. Additional information was linked from the pelvic pouch database on patients' demographics, disease history, and technical characteristics of the operation</p>	
Participants	<p>Participants included female patients with UC or familial adenomatous polyposis who underwent pelvic pouch operation and were 15 to 44 years of age at the time of operation. 206 out of 300 participants who responded attempted to conceive before and/or after restorative proctocolectomy with IPAA (127 before operation, 135 after operation, and 56 before and after operation). Of the 206 included women, 185 had UC, with 117 attempting to conceive before surgery, 120 attempting to conceive after surgery, and 52 attempting to conceive both before and after pregnancy</p>	
Interventions	Before and after restorative proctocolectomy with IPAA	
Outcomes	<p>PRIMARY OUTCOME: Infertility was defined as 1 year of unprotected intercourse without conception for women who tried to get pregnant</p> <p>SECONDARY OUTCOME: Use of ART</p>	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients with UC who tried to conceive after undergoing restorative proctocolectomy with IPAA, identified in the pelvic pouch database from a single center in Cleveland, Ohio. This study was identified as having high risk of bias because participants were identified from a tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients who tried to conceive before undergoing restorative proctocolectomy with IPAA, identified from the same center as the exposed cohort. This study was identified as having high risk of bias because participants were identified from a tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained from the pelvic pouch database
Outcome of interest was not present at start of study (selection bias)	Low risk	Fertility status was determined before and after surgery

Gorgun 2004 (Continued)

Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Information on infertility was obtained from the self-reported questionnaire that was mailed to participants
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Fertility was determined for 1 year of unprotected intercourse
Adequacy of follow up cohorts (outcome)	High risk	300/500 (60%) female patients responded to the questionnaire

Hahnloser 2004

Methods	STUDY DESIGN: This was a cross-sectional study conducted between 1981 and 1995 DATA COLLECTION: Standardized questionnaires were sent to participants identified from a prospectively managed database. The questionnaire included information on outcomes and complications of pregnancy and delivery before and after IPAA (e.g. method of delivery, length of labor, birth weight). Additional information was obtained from the prospectively collected database
Participants	Participants included 544 female patients who underwent IPAA for UC and were < 40 years of age at the time of surgery. All patients underwent colectomy, complete mobilization of the small bowel mesentery, and proximal rectal mobilization using a close rectal dissection technique
Interventions	The intervention of interest was before and after IPAA. IPAA involved excising the anal transition zone and hand-sewing the pouch to the anal canal or preserving the anal transition zone and double-stapling the pouch to the anal canal. All patients had a diverting ileostomy constructed, which was closed between 2 and 3 months after IPAA
Outcomes	SECONDARY OUTCOMES: Miscarriage, stillbirth, gestational diabetes, preeclampsia
Notes	Results are presented for the subgroup of 37 women who were pregnant before and after surgery. Data on pregnancy-related outcomes before IPAA are described per woman, and data on pregnancy-related outcomes after IPAA are described per pregnancy

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	Unclear risk	The exposed cohort consisted of female patients who were pregnant after undergoing IPAA for UC, identified from a prospectively managed database from Switzerland. Study authors do not describe how participants were identified for inclusion in the database
Selection of the non-exposed cohort (selection bias)	Unclear risk	The non-exposed cohort consisted of female patients who were pregnant before undergoing IPAA for UC, identified from a prospectively managed database from Switzerland. Study authors do not describe how participants were identified for inclusion in the database
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained from the prospective database

Hahnloser 2004 (Continued)

Outcome of interest was not present at start of study (selection bias)	Low risk	Pregnancy status was determined by the questionnaire to assess pregnancy outcomes
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Information on pregnancy outcomes was obtained through questionnaire and the prospectively collected database. This study was identified as having high risk of bias because some outcome data were obtained from self-report
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Mean follow-up after IPAA was 13 years
Adequacy of follow up cohorts (outcome)	Low risk	450/544 (82.7%) responded to the questionnaire

Hudson 1997

Methods	<p>STUDY DESIGN: This was a cross-sectional* study conducted between 1967 and 1986 at a large teaching hospital (i.e. single referral center for gastroenterology, obstetrics, and pathology) in North East of Scotland, including the Orkney and Shetland Isles, with a stable population of 600,000 during the study period</p> <p>DATA COLLECTION: A 4-page anonymous questionnaire was sent with a prepaid return envelope. The questionnaire assessed menstruation, past and current contraceptive status, desire for pregnancy, date of each delivery, pregnancy outcomes, and any conception difficulty. Additional information was obtained through hospital medical or obstetric records, and if necessary, from the general practitioner</p>
Participants	<p>Women 16 to 45 years of age with an established diagnosis of CD or UC based on accepted clinical, radiologic, endoscopic, and/or histologic appearance and residents in the Grampian Region for at least 6 months before onset of symptoms (n = 466). 409 women completed the questionnaire (CD: n = 177; UC: n = 232), and infertility was assessed among women who were potentially fertile (CD: n = 123; UC: n = 138). Involuntary infertility was assessed in 86 women with CD and 104 women with UC. Among women included in the study, there were 132 pregnancies, of which 79 occurred in women without previous surgery, 39 in women with previous surgery but no evidence of endoscopic or radiologic evidence of active disease at conception, and 14 in women who had had previous surgery and evidence of disease recurrence at conception</p>
Interventions	<p>The intervention of interest was surgical vs medical management of IBD. Details of both surgical and medical management are not specifically discussed in the study</p>
Outcomes	<p>PRIMARY OUTCOME: Infertility was defined as unsuccessfully achieving a desired spontaneous conception after 24 months of unprotected intercourse</p> <p>SECONDARY OUTCOMES: Miscarriage (spontaneous abortion), stillbirth, premature delivery</p>
Notes	<p>Data on secondary outcomes were reported only for women with CD</p> <p>*The study authors reported this as a retrospective study. Participants were identified retrospectively but the questionnaire was sent to all participants at the time of the study; this should therefore be described as a cross-sectional study</p>

Risk of bias

Hudson 1997 (Continued)

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	Low risk	All women had established diagnosis of UC or CD and underwent surgical treatment for IBD in the Grampian region. This region is serviced by a single referral center
Selection of the non-exposed cohort (selection bias)	Low risk	All women had established diagnosis of IBD and received medical treatment in the Grampian region. This region is serviced by a single referral center
Ascertainment of exposure (selection bias)	High risk	A 4-page anonymous questionnaire was reviewed along with additional information from hospital medical or obstetric records. This study was identified as having high risk because some exposure data were obtained from self-report
Outcome of interest was not present at start of study (selection bias)	Low risk	Females were selected based on disease status and then provided information on infertility and pregnancy-related outcomes
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	A 4-page anonymous questionnaire was reviewed with additional information from hospital medical or obstetric records. This study was identified as having high risk of bias because some outcome data were obtained from self-report
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Follow-up was not reported, but infertility was assessed at 24 months
Adequacy of follow up cohorts (outcome)	Low risk	There were 409/466 (88%) women who replied to the study questionnaire (UC: 232; CD: 177). Of the 57 who did not reply, none had sought hospital investigation for infertility

Johnson 2004

Methods	<p>STUDY DESIGN: This was a cross-sectional study conducted at Mount Sinai Hospital in Toronto, Canada</p> <p>DATA COLLECTION: Information included in the IBD database at Mount Sinai Hospital was prospectively collected. A questionnaire was mailed to all female patients with UC who were non-operatively managed or had a previous IPAA. Patients were called to encourage a reply and to clarify any missing data</p>
Participants	All 560 female patients with UC were registered in the IBD database at Mount Sinai Hospital in Toronto, Canada (non-operatively managed: n = 237; IPAA for UC: n = 323). Eligibility criteria included ≥ 18 years of age at the time of the study, < 44 years of age at the time of IPAA or diagnosis with UC, and married or cohabitating for at least 12 months after surgery or diagnosis (non-operatively managed: n = 60; IPAA for UC: n = 153). Patients with incomplete data regarding relationship history and reproductive history were excluded
Interventions	<p>IPAA vs medical treatment (non-operatively managed)</p> <p>Before and after IPAA</p>
Outcomes	PRIMARY OUTCOME: Infertility was defined as failure to become pregnant during 12 months of unprotected intercourse. Only women who attempted pregnancy were considered

Johnson 2004 (Continued)

SECONDNDARY OUTCOME: Use of ART

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients with UC who underwent IPAA and were registered in the Inflammatory Bowel Disease database at Mount Sinai Hospital, in Toronto. This study was identified as having high risk of bias because participants were identified from a single tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients with UC who were non-operatively managed and were registered in the same database as the exposed cohort. This study was identified as having high risk of bias because participants were identified from a tertiary care center
Ascertainment of exposure (selection bias)	Unclear risk	Females had IPAA for UC and were registered in the Inflammatory Bowel Disease database at Mount Sinai Hospital, in Toronto. Study authors did not specifically describe how information on patients' surgical history was identified in the database
Outcome of interest was not present at start of study (selection bias)	Low risk	Pregnancy status was determined by questionnaire responses
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	A questionnaire, including information on infertility, was mailed to participants. This study was identified as having high risk of bias because some outcome data were obtained from self-report
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Mean (SD) duration of follow-up after IPAA was 11.6 (4) (range 5.8 to 20.9) years. In those with non-operatively managed UC, mean (SD) duration of follow-up after diagnosis was 15.6 (10.7) (range 4.7 to 57.8) years
Adequacy of follow up cohorts (outcome)	High risk	Of females who had IPAA, 254/323 (78.6%) completed and returned the questionnaire and 153 (60.2%) met the inclusion criteria. Of females with non-operatively managed UC, 143/237 (60.3%) completed and returned the questionnaire and 60 (42.0%) met the inclusion criteria

Koivusalo 2009

Methods	<p>STUDY DESIGN: This was a cross-sectional study conducted at 2 major university hospitals (Helsinki and Tampere) in Finland</p> <p>DATA COLLECTION: Data were collected via a self-reported questionnaire during a follow-up outpatient visit. The questionnaire collected information on sexual function, bowel function, stool frequency, fecal incontinence, and medication. Time of data collection was not reported</p>
Participants	Eligible participants were treated at 1 of 2 major university hospitals between 1985 and 2005. Participants included 25 patients (17 females) with pediatric-onset UC (< 16 years) who underwent restorative proctocolectomy with ileoanal anastomosis and who were sexually active and > 16 years of age at the

Koivusalo 2009 (Continued)

time of the study. Controls included 38 sexually active medically treated UC patients (19 females) > 16 years of age at the time of the study

Interventions	Restorative proctocolectomy with ileoanal anastomosis compared to pharmacologic treatment
Outcomes	PRIMARY OUTCOME: Infertility was defined as not becoming pregnant within 12 months after trying to conceive
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of patients with pediatric-onset UC who underwent restorative proctocolectomy with ileoanal anastomosis and were > 16 years of age and sexually active at the time of the study. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of patients from the same outpatient clinic who were medically treated and were > 16 years of age and sexually active. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Ascertainment of exposure (selection bias)	Unclear risk	Study authors did not specifically describe how previous surgical history was obtained, but exposed and non-exposed study participants were recruited based on their surgical history
Outcome of interest was not present at start of study (selection bias)	Low risk	Questionnaire asks whether participants became pregnant
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Only descriptive statistics are reported
Assessment of outcome (outcome)	High risk	Questionnaire was given to participants during follow-up visits
Was follow-up long enough for outcomes to occur (outcome)	Unclear risk	This was not reported
Adequacy of follow up cohorts (outcome)	High risk	Of 81 patients eligible for the study, 79 patients were invited back to participate. Of these, 36 (49.4%) attended the follow-up outpatient visit

Mortier 2006

Methods	STUDY DESIGN: This was a cross-sectional study conducted between May and September 2003 DATA COLLECTION: Data were collected by telephone structured interviews conducted by instructed and trained female interviewers
Participants	Eligible participants were treated in the Department of Abdominal Surgery at the Centre Hospitalier Régional, Université de Lille, in Lille, France, between 1962 and 1999. Participants of interest included 37

Mortier 2006 (Continued)

female patients who underwent ileorectal anastomosis for UC. Women were excluded for the following reasons: died from a postoperative complication or alcoholic cirrhosis (n = 2), confirmed diagnosis of CD (n = 5), and proctectomy for rectal cancer (n = 1)

Interventions	Before and after total colectomy with an ileorectal anastomosis
Outcomes	PRIMARY OUTCOME: Proportion of those pregnant with unprotected intercourse at 6, 12, and 24 months SECONDARY OUTCOME: Time to pregnancy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients who underwent ileorectal anastomosis for UC at a single center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients who did not have ileorectal anastomosis for UC and were treated at the same single center
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained from the hospital record
Outcome of interest was not present at start of study (selection bias)	Low risk	Pregnancy status was determined during data collection
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Telephone interviews were conducted to assess infertility
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Median follow-up was 16 (range 4 to 35) years
Adequacy of follow up cohorts (outcome)	Low risk	No patients were lost to follow-up

Moser 2000

Methods	STUDY DESIGN: This was a retrospective study conducted in Edmonton, Canada, from January 1993 to December 1997 DATA COLLECTION: Data were collected by reviewing the detailed recording of data on prenatal sheets, the discharge data summary, and the neonate history and physical. Reference was made to the admission medical history, the nursing history, and the patient history
Participants	Participants were included in the study if they met the following criteria: patients' charts were coded for pregnancy and inflammatory bowel disease, Crohn's disease, or a gastrointestinal (GI) consultation (n = 91). Participants were excluded if they met either of the following criteria: (1) admission for missed

Moser 2000 (Continued)

abortion, therapeutic abortion, or spontaneous abortion before 20 weeks (n = 23); and (2) active disease at the time of conception (n = 5). A total of 65 female patients with CD had pregnancy that went beyond 32 weeks (76 pregnancies). Among those with multiple pregnancies, only one pregnancy was selected at random. These 65 pregnancies among female patients with CD were matched to pregnancies among healthy controls from the Northern Alberta Perinatal Outreach Program database based on maternal age, parity, smoking status, approximate date of delivery, and gestational age

Interventions	Previous surgery vs no surgery (i.e. medical treatment)
Outcomes	SECONDARY OUTCOME: Small for gestational age neonates (birth weight falling below the 10th percentile)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients with CD with previous surgery who were identified from retrospective chart review at a single center. This study was identified as having high risk of bias because it included participants from a single tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients with CD without previous surgery who were identified from retrospective chart review at the same single center. This study was identified as having high risk of bias because it included participants from a single tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Surgery records were obtained from chart review
Outcome of interest was not present at start of study (selection bias)	Low risk	Pregnancy status was determined from patients' charts
Comparability of cohorts on the basis of the design or analysis (comparability)	Low risk	Adjusted for ileal disease location (ileal or ileocolonic), smoking during pregnancy, and poor maternal weight gain
Assessment of outcome (outcome)	Low risk	Information on small for gestational age infants was obtained through chart review
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Retrospective chart review included a 5-year period
Adequacy of follow up cohorts (outcome)	Low risk	Retrospective chart review – all patients meeting the eligible criteria were included

Naganuma 2011

Methods	<p>STUDY DESIGN: This was a cross-sectional* study conducted at 6 large IBD centers in Japan</p> <p>DATA COLLECTION: Questionnaires were given to participants. Questionnaires collected information on type of disease, marital status, number of children, smoking habits, age at each conception, history of surgery for IBD, history of surgery for perianal lesions, abscesses and fissuring ulcerations in CD patients, history of therapy for infertility, outcomes of conceptions, mode of delivery, birth weight, and</p>
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Naganuma 2011 (Continued)

presence of congenital abnormalities. Female patients, when pregnant, were also given a notebook to report information regarding conception and outcome of pregnancy. Information on pregnancy course and outcomes, as well as birth weight, was provided by physicians or nurses. Medical records were reviewed to confirm diagnosis of disease, continuation or discontinuation of medications at the time of conception, conception outcomes, mode of delivery, and congenital malformation

Participants	Study participants were women with IBD treated at 1 of the 6 large IBD centers in Japan and conceived between 1989 and 2008. The study included 572 female IBD patients (CD: n = 247; UC: n = 325); 325 (CD: n = 80; UC: n = 245) between the ages of 17 and 46 years who experienced conception at least once were selected. No patients experienced ovarian cancer or uterine cancer. A total of 534 conceptions were observed, of which 303 (CD: n = 69; UC: n = 234) occurred during or after disease onset
Interventions	Previous surgery vs no previous surgery (medical management only)
Outcomes	SECONDARY OUTCOMES: miscarriage (spontaneous abortion), mode of delivery (i.e. Caesarean delivery vs vaginal delivery), low birth weight (< 2500 g)
Notes	*Study authors reported this as a retrospective study. Participants were identified retrospectively, but the questionnaire was sent to all participants at the time of the study. This should therefore be described as a cross-sectional study

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients with IBD from the 6 large IBD centers in Japan who had previous surgery for IBD and conceived during or after disease onset. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients with IBD from the same 6 large IBD centers in Japan who did not have previous surgery for IBD and conceived during or after disease onset. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Ascertainment of exposure (selection bias)	Low risk	Questionnaire and notebook were used, and information was confirmed by medical records
Outcome of interest was not present at start of study (selection bias)	Low risk	Retrospective study; conception was determined in selecting patients
Comparability of cohorts on the basis of the design or analysis (comparability)	Low risk	Multivariable analysis was adjusted for mother's height (< 150 cm), mother's age at conception (> 35 years old), smoking, history of previous treatment for infertility, and history of gynecologic disease
Assessment of outcome (outcome)	Low risk	Notebook was used to record pregnancy outcomes by mothers and physicians or nurses; information was then confirmed by medical records
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Participants were followed from conception to birth
Adequacy of follow up cohorts (outcome)	Low risk	11/589 (1.9%) patients refused to participate in the study

Nielsen 1984

Methods	<p>STUDY DESIGN: This was a retrospective cohort study conducted in patients from outpatient clinics or admitted between January 1968 and December 1980</p> <p>DATA COLLECTION: Information was obtained from medical records. Women with insufficient data were contacted by telephone</p>
Participants	Eligible participants were treated at outpatient clinics or were admitted to hospital between January 1968 and December 1980. Participants included 68 women (109 pregnancies included; 40 pregnancies took place before the study period or pregnancies had ended 6 months before the onset of disease) with CD under the age of 37 years at the time of conception who were pregnant during the study period and had been diagnosed with CD after the onset of disease
Interventions	Previous IBD surgery vs no previous IBD surgery
Outcomes	SECONDARY OUTCOMES: Stillbirth, preterm birth, miscarriage (spontaneous abortion)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of pregnant female patients with CD < 37 years of age at the time of conception who were diagnosed with CD before pregnancy and had previous resection of the bowel that had been treated at a single center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of pregnant female patients with CD < 37 years of age at the time of conception who were diagnosed with CD before pregnancy and did not have previous resection of the bowel and were treated at the same single center. This study was identified as having high risk of bias because participants were identified from a tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Surgery information was obtained from medical records and patients were contacted by telephone when medical records included insufficient data
Outcome of interest was not present at start of study (selection bias)	Low risk	Females were selected into the study based on their pregnancy status. Study excluded women who did not have pregnancies during the 13-year period
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	Low risk	Secondary outcomes were obtained from medical records and patients were contacted by telephone when data were insufficient
Was follow-up long enough for outcomes to occur (outcome)	Low risk	The study period was 13 years
Adequacy of follow up cohorts (outcome)	Low risk	All eligible participants in the study were accounted for to conduct analyses

Olsen 2002

Methods	<p>STUDY DESIGN: This was a prospective cohort study conducted at 4 participating centers in Denmark and Sweden (Swedish Colorectal Unit, Sahlgrenska, University Hospital Gothenberg; Danish Surgical Department C, Rigshospitalet, Copenhagen; Danish Surgical Department L, Aarhus University Hospital; Danish Surgical Department A, Odense University Hospital)</p> <p>DATA COLLECTION: Data were collected by telephone interviews using a highly structured interview form conducted by thoroughly trained female interviewers before diagnosis of UC (before diagnosis), from diagnosis until colectomy (before colectomy), and from stoma closure until the date of the interview (after IPAA). Participants were asked about their first interval of unprotected intercourse starting within each time/age window, reproductive history, starting and ending dates (or duration) in each time window, intent to become pregnant (planning), and exposures around the starting date of this first time interval</p>
Participants	Eligible patients were treated at 1 of the 4 participating centers between November 1982 and January 1998. The study included 343 women with UC who underwent restorative proctocolectomy with IPAA, were ≤ 40 years old at the time of stoma closure, and were > 18 years of age at the time of the interview. A reference population of 1200 women aged 25 to 50 years was drawn at random from the national population registers of Denmark and Sweden to serve as a primary comparison between women with and without UC. There were 290 participating patients who gave information (98 before diagnosis, 84 before colectomy, and 149 after IPAA)
Interventions	Before and after restorative proctocolectomy with IPAA
Outcomes	PRIMARY OUTCOME: Infertility was defined as the inverse of the probability of becoming pregnant after 12 and 24 months of unprotected intercourse
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	This study was identified as having high risk of bias because participants were identified from tertiary care centers
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients with UC from the same 4 tertiary care centers who did not have restorative proctocolectomy with IPAA. This study was identified as having high risk of bias because participants were identified from tertiary care centers
Ascertainment of exposure (selection bias)	High risk	Information on surgical intervention was obtained through telephone interviews conducted by trained interviewers
Outcome of interest was not present at start of study (selection bias)	Low risk	Women were identified based on surgical status, and pregnancy status was determined
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Information on infertility was obtained through a telephone interview
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Women were followed for more than a year before or after surgery

Olsen 2002 (Continued)

Adequacy of follow up cohorts (outcome)	High risk	290/393 (73.8%) participating patients gave information. No description of non-participating women was provided
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Ravid 2002

Methods	<p>STUDY DESIGN: This was a cross-sectional study conducted at a single center</p> <p>DATA COLLECTION: Questionnaires on infertility, pregnancy, type of delivery, birth weight of the baby, and complications of pregnancy and pouch were sent to identified participants. Females who had become pregnant after IPAA and gave birth at least once after IPAA were further contacted by telephone</p>	
Participants	<p>Eligible participants were treated at the Inflammatory Bowel Disease Unit of Mount Sinai Hospital in Toronto, Ontario, Canada, between 1982 and 1998. Participants of interest were 38/481 females (average age of 32 at operation) who underwent IPAA at the Inflammatory Bowel Disease Unit of Mount Sinai Hospital and became pregnant after IPAA. Of those participating, 26 had a stapled J-pouch and 12 had an S-pouch; 18 had a 3-stage operation, 18 had a 2-stage operation, and 2 had a 1-stage operation; and 17 ileoanal anastomoses were handsewn and 21 were stapled. Nine were without loop ileostomy</p>	
Interventions	Before and after IPAA	
Outcomes	SECONDARY OUTCOMES: Mode of delivery, miscarriage, stillbirth	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients with UC who underwent IPAA and became pregnant at a single tertiary care center. This study was identified as having high risk of bias because participants were recruited from a tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients with UC who were pregnant before IPAA and were identified from the same tertiary care center. This study was identified as having high risk of bias because participants were recruited from a tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained from the database at the IBD clinic
Outcome of interest was not present at start of study (selection bias)	Low risk	Pregnancy status was identified
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Pregnancy outcomes were obtained through a self-reported questionnaire and by telephone interview
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Patients were followed through the whole pregnancy

Ravid 2002 (Continued)

Adequacy of follow up cohorts (outcome) Low risk 400/481 (83%) female patients responded

Tulchinsky 2013

Methods	<p>STUDY DESIGN: This was a cross-sectional study conducted at a comprehensive pouch clinic (tertiary referral center for pouch patients) in Israel</p> <p>DATA COLLECTION: Participants were contacted during visits to the clinic or by telephone. Eligible participants filled out a questionnaire on infertility, pregnancy, delivery, and newborn status and addressed issues on time to conceive, the need for infertility therapies, medical treatment before and during pregnancy, miscarriage, duration of pregnancy, and pregnancy-related complications. Additional information (i.e. patients' demographics, past medical history, and operations) was collected from the pouch clinic's database and during patient visits</p>
Participants	Participants included women who underwent restorative proctocolectomy before the age of 45 years and were ≥ 21 years of age at the time of the study and were attempting or had attempted to become pregnant before and/or after restorative proctocolectomy
Interventions	Before and after restorative proctocolectomy
Outcomes	<p>PRIMARY OUTCOME: Infertility was defined as the inability to achieve conception after 1 year of unprotected sex with a fertile male partner</p> <p>SECONDARY OUTCOMES: Use of ART, mode of delivery, time to pregnancy, miscarriage</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of female patients with UC identified from a single tertiary care center who were attempting or attempted to conceive after undergoing restorative proctocolectomy. This study was identified as having high risk of bias because participants were recruited from a tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of female patients with UC identified at the same tertiary care center who were attempting or attempted to conceive before undergoing restorative proctocolectomy. This study was identified as having high risk of bias because participants were recruited from a tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained from the pouch clinic's database
Outcome of interest was not present at start of study (selection bias)	Low risk	Females were selected into the study based on their pregnancy status
Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	High risk	Information on infertility and pregnancy outcomes was obtained through a self-reported questionnaire and linkage to the pouch clinic's database. This

Tulchinsky 2013 (Continued)

		study was identified as having high risk of bias because some outcome data were obtained by self-report
Was follow-up long enough for outcomes to occur (outcome)	Low risk	Infertility was observed at 1 year, and pregnancies were followed through until the end
Adequacy of follow up cohorts (outcome)	Low risk	41 of 47 (87.2%) returned the questionnaire

Zavorova 2017

Methods	<p>STUDY DESIGN: This was a retrospective cohort study conducted in the Department of Obstetrics and Gynecology, Hospital Horovice, Czech Republic, between October 2014 and March 2016</p> <p>DATA COLLECTION: Data on infertility, pregnancy, therapy in pregnancy, and mode of delivery were included</p>	
Participants	<p>Participants included 17 patients with varying degrees of disability due to IBD (including patients after previous surgeries for bowel resection, hemicolectomy, or ileostomy, or with a pouch) who gave birth in the Department of Obstetrics and Gynecology, Hospital Horovice. There were 12 patients with CD who had 14 births, of whom 7 patients (9 births) had not had previous surgery and 5 patients (5 births) had had previous CD-related intestinal resection. Ten women with CD were using medication during pregnancy (mesalazine: n = 2; combination of mesalazine and budesonide: n = 1; azathioprine: n = 3; azathioprine and adalimumab: n = 1; infliximab monotherapy: n = 1; adalimumab monotherapy: n = 2). There were 5 patients with UC with 6 births; 2 patients (2 births) became pregnant after surgery for IPAA; and 3 patients (4 births) were without previous surgery (2 women were on mesalazine and 1 was not taking any medication)</p>	
Interventions	<p>Previous surgery for IBD or no previous surgery. Surgery for UC was IPAA, and surgery for CD was a mix of colectomy with terminal ileostomy, ileocecal resection with anastomosis, and other procedures</p>	
Outcomes	<p>SECONDARY OUTCOMES: Caesarean section, low birth weight, prematurity</p>	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Representativeness of cohort (selection bias)	High risk	The exposed cohort consisted of patients with CD or UC after surgery identified from a single tertiary care center. This study was identified as having high risk of bias because participants were recruited from a tertiary care center
Selection of the non-exposed cohort (selection bias)	High risk	The non-exposed cohort consisted of patients with CD or UC without previous surgery identified from the same tertiary care center. This study was identified as having high risk of bias because participants were recruited from a tertiary care center
Ascertainment of exposure (selection bias)	Low risk	Information on surgical intervention was obtained from the hospital database
Outcome of interest was not present at start of study (selection bias)	Low risk	Females were selected into the study and pregnancy status was determined

Zavorova 2017 *(Continued)*

Comparability of cohorts on the basis of the design or analysis (comparability)	High risk	Unadjusted
Assessment of outcome (outcome)	Low risk	Females were selected into the study and pregnancy status was determined
Was follow-up long enough for outcomes to occur (outcome)	Unclear risk	This was not reported
Adequacy of follow up cohorts (outcome)	Unclear risk	No loss to follow-up was reported

ART: assisted reproductive technology.

CD: Crohn's disease.

IBD: inflammatory bowel disease.

IPAA: ileal pouch anal anastomosis.

SD: standard deviation.

UC: ulcerative colitis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allan 1994	Review article, editorial/commentary, or clinical practice guidelines
Alstead 2001	Review article, editorial/commentary, or clinical practice guidelines
Amate 2011	Review article, editorial/commentary, or clinical practice guidelines
Anania 1997	Review article, editorial/commentary, or clinical practice guidelines
Andrews 2010	Review article, editorial/commentary, or clinical practice guidelines
Anniciello 2007	Review article, editorial/commentary, or clinical practice guidelines
Balzola 2011	Review article, editorial/commentary, or clinical practice guidelines
Ban 2015	No data on infertility or a secondary outcome included
Barwin 1974	No data on infertility or a secondary outcome included
Bauer 1986	No data on infertility or a secondary outcome included
Bertaud 1967	Case report or case series
Beyer-Berjot 2013	Findings not limited to patients with IBD
Bharadwaj 2014	Review article, editorial/commentary, or clinical practice guidelines
Bielecki 2006	Case report or case series
Bradford 2014	No data on infertility or a secondary outcome included

Study	Reason for exclusion
Broms 2012	No data on infertility or a secondary outcome included
Campillos Realí 1971	Case report or case series
Cave 1946	Case report or case series
Cima 2007	Review article, editorial/commentary, or clinical practice guidelines
Cleandre 1993	Case report or case series
Coffey 2002	No data on infertility or a secondary outcome included
Cornish 2011	Findings not limited to patients with IBD
Counihan 1994	Findings not limited to patients with IBD
Couve 2003	Review article, editorial/commentary, or clinical practice guidelines
Da Fonseca 2008	Review article, editorial/commentary, or clinical practice guidelines
Dalal 2012	No data on infertility or a secondary outcome included
Daly 1967	No data on infertility or a secondary outcome included
De Carolis 2004	Review article, editorial/commentary, or clinical practice guidelines
De Dombal 1965	Neither infertility nor secondary outcomes described in comparison group
de Saussure 2006	Review article, editorial/commentary, or clinical practice guidelines
Delaini 1985	Review article, editorial/commentary, or clinical practice guidelines
Dozois 1993	Review article, editorial/commentary, or clinical practice guidelines
Drobni 1972	Case report or case series
Dubinsky 2007	Review article, editorial/commentary, or clinical practice guidelines
Dubinsky 2008	Review article, editorial/commentary, or clinical practice guidelines
Duzhyi 2006	Case report or case series
Eglinton 2007	Review article, editorial/commentary, or clinical practice guidelines
Evans 2012	Review article, editorial/commentary, or clinical practice guidelines
Farouk 2000	No data on infertility or a secondary outcome included
Ferguson 2008	Review article, editorial/commentary, or clinical practice guidelines
Ferla 1988	Review article, editorial/commentary, or clinical practice guidelines
Filippi 2009	Review article, editorial/commentary, or clinical practice guidelines
Friedman 2001	Review article, editorial/commentary, or clinical practice guidelines

Study	Reason for exclusion
Friedman 2002	Review article, editorial/commentary, or clinical practice guidelines
Friedman 2015	Review article, editorial/commentary, or clinical practice guidelines
Frise 2013	Review article, editorial/commentary, or clinical practice guidelines
Goettler 2003	Review article, editorial/commentary, or clinical practice guidelines
Gross 1994	Review article, editorial/commentary, or clinical practice guidelines
Grouin 2015	No data on infertility or a secondary outcome included
Grüner 1977	No data on infertility or a secondary outcome included
Hanan 1998	Review article, editorial/commentary, or clinical practice guidelines
Harnoy 2016	No eligible comparison group included
Hartmann 1965	Review article, editorial/commentary, or clinical practice guidelines
Holubar 2011	Review article, editorial/commentary, or clinical practice guidelines
Hor 2016	Findings not limited to patients with IBD
Huang 2014	Review article, editorial/commentary, or clinical practice guidelines
Hudson 1972	No eligible comparison group included
Hudson 1973	No eligible comparison group included
Isaacs 2014	Review article, editorial/commentary, or clinical practice guidelines
Izanec 2006	Review article, editorial/commentary, or clinical practice guidelines
Jalocha 2010	Review article, editorial/commentary, or clinical practice guidelines
Johnson 2006	Review article, editorial/commentary, or clinical practice guidelines
Johnson 2008	Review article, editorial/commentary, or clinical practice guidelines
Juhasz 1995	No data on infertility or a secondary outcome included
Kalkan 2012	Review article, editorial/commentary, or clinical practice guidelines
Kane 2006	Review article, editorial/commentary, or clinical practice guidelines
Karthouser 2006	Review article, editorial/commentary, or clinical practice guidelines
Keighley 1993	No data on infertility or a secondary outcome included
Kelly 1994	Case report or case series
Kitayama 2005	No eligible comparison group included
Koganei 1999	Case report or case series

Study	Reason for exclusion
Korelitz 1998	Review article, editorial/commentary, or clinical practice guidelines
Kukulska 2013	Review article, editorial/commentary, or clinical practice guidelines
Lapinska 1994	Review article, editorial/commentary, or clinical practice guidelines
Larson 2007	Review article, editorial/commentary, or clinical practice guidelines
Lehur 1995	No data on infertility or a secondary outcome included
Lepisto 2007	Comparison of patients with IBD vs non-IBD controls
Lindhagen 1986	No data on infertility or a secondary outcome included
Long 2015	Review article, editorial/commentary, or clinical practice guidelines
Lukas 2001	Review article, editorial/commentary, or clinical practice guidelines
Mahadevan 2006a	Review article, editorial/commentary, or clinical practice guidelines
Mahadevan 2006b	Review article, editorial/commentary, or clinical practice guidelines
Mahadevan 2009	Review article, editorial/commentary, or clinical practice guidelines
Martin 2016	Review article, editorial/commentary, or clinical practice guidelines
McEwan 1965	Case report or case series
McEwan 1972	No data on infertility or a secondary outcome included
McLaughlin 2008	Review article, editorial/commentary, or clinical practice guidelines
McLeod 2008	Review article, editorial/commentary, or clinical practice guidelines
Metcalf 1985	Case report or case series
Metcalf 1986	Findings not limited to patients with IBD
Michelassi 1993	No data on infertility or a secondary outcome included
Munie 2013	No data on infertility or a secondary outcome included
Nielsen 1983	No data on infertility or a secondary outcome included
Nowak 1989	Review article, editorial/commentary, or clinical practice guidelines
Olsen 1999	No data on infertility or any secondary outcome included
Olsen 2003	Patients with IBD not included
Oresland 1994	No data on infertility or any secondary outcome included
Osathanondh 1979	Case report or case series
Oza 2016	No data on infertility or a secondary outcome included

Study	Reason for exclusion
Pabby 2015	No data on infertility or a secondary outcome included
Pachler 2017	No data on infertility or a secondary outcome included
Peppercorn 2000	Review article, editorial/commentary, or clinical practice guidelines
Pezim 1984	Case report or case series
Priest 1959	Case report or case series
Rajaratnam 2011	Review article, editorial/commentary, or clinical practice guidelines
Ramalingam 2003	Review article, editorial/commentary, or clinical practice guidelines
Reme 1974	Review article, editorial/commentary, or clinical practice guidelines
Richard 2013	Review article, editorial/commentary, or clinical practice guidelines
Ritchie 1971	No data on infertility or a secondary outcome included
Sachsenmaier 1988	Review article, editorial/commentary, or clinical practice guidelines
Santos 1993	Review article, editorial/commentary, or clinical practice guidelines
Scaglia 1992	No data on infertility or any secondary outcome included
Scaglia 1993	No data on infertility or any secondary outcome included
Scott 1996	Findings not limited to patients with IBD
Selinger 2013	Review article, editorial/commentary, or clinical practice guidelines
Sjorgren 1995	No data on infertility or any secondary outcome included
Stein 2008	Review article, editorial/commentary, or clinical practice guidelines
Sur 2013	Case report or case series
Takahashi 2007	Case report or case series
Tiainen 1999	No eligible comparison group included
Tinneberg 2013	Review article, editorial/commentary, or clinical practice guidelines
Trachter 2002	Review article, editorial/commentary, or clinical practice guidelines
Villet 2005	Review article, editorial/commentary, or clinical practice guidelines
Wang 1993	Case report or case series
Warren 1948	Case report or case series
Warsof 1983	Review article, editorial/commentary, or clinical practice guidelines
Wax 2003	Review article, editorial/commentary, or clinical practice guidelines

Study	Reason for exclusion
Webb 1974	Review article, editorial/commentary, or clinical practice guidelines
Weterman 1989	Review article, editorial/commentary, or clinical practice guidelines
Wikland 1990	No data on infertility or any secondary outcome included
Willoughby 1980	Women with a history of surgery before pregnancy excluded
Wilson 1964	No data on infertility or a secondary outcome included
Witherspoon 2010	Case report or case series
Wolf 2002	Review article, editorial/commentary, or clinical practice guidelines
Wolters 2006	No data on infertility or a secondary outcome included

IBD: inflammatory bowel disease.

DATA AND ANALYSES

Comparison 1. Any surgery versus no surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infertility at 12 Months	2	114	Risk Ratio (M-H, Random, 95% CI)	5.45 [0.41, 72.57]
2 Infertility at 24 Months	1	190	Risk Ratio (M-H, Random, 95% CI)	3.59 [1.32, 9.73]
2.1 Crohn's Disease	1	86	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.56, 7.33]
2.2 Ulcerative Colitis	1	104	Risk Ratio (M-H, Random, 95% CI)	5.28 [2.09, 13.34]
3 Miscarriage	5	776	Odds Ratio (Random, 95% CI)	2.03 [1.14, 3.60]
3.1 Crohn's Disease	3	386	Odds Ratio (Random, 95% CI)	2.56 [1.19, 5.51]
3.2 Ulcerative Colitis	1	87	Odds Ratio (Random, 95% CI)	7.14 [1.02, 50.18]
3.3 IBD	1	303	Odds Ratio (Random, 95% CI)	1.20 [0.54, 2.67]
4 Miscarriage - Sensitivity Analysis Based on Source of Participants	5		Odds Ratio (Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Population-Based	1	132	Odds Ratio (Random, 95% CI)	2.79 [1.11, 7.04]
4.2 Tertiary Care	4	644	Odds Ratio (Random, 95% CI)	1.84 [0.84, 4.03]
5 Miscarriage - Sensitivity Analysis Including Only Women in Remission at Conception	2	173	Risk Ratio (M-H, Random, 95% CI)	2.38 [1.11, 5.11]
6 Stillbirth	3	246	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.42, 9.18]
6.1 Crohn's Disease	2	174	Risk Ratio (M-H, Random, 95% CI)	1.98 [0.32, 12.16]
6.2 Ulcerative Colitis	1	72	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.10, 36.02]
7 Stillbirth - Sensitivity Analysis Based on Source of Participants	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Population-Based	1	94	Risk Ratio (M-H, Random, 95% CI)	5.47 [0.23, 130.65]
7.2 Tertiary Care	2	152	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.24, 8.35]
8 Stillbirth - Sensitivity Analysis Including Only Women in Remission at Conception	2	136	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.07, 23.54]
9 Use of ART	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Caesarean Section	1	20	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.00, 4.95]
10.1 Crohn's Disease	1	14	Risk Ratio (M-H, Random, 95% CI)	3.60 [0.98, 13.19]
10.2 Ulcerative Colitis	1	6	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.61, 4.59]
11 Preterm Delivery	3	194	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.67, 5.48]
11.1 Crohn's Disease	3	188	Risk Ratio (M-H, Random, 95% CI)	2.32 [0.75, 7.21]
11.2 Ulcerative Colitis	1	6	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.03, 9.73]
12 Preterm Delivery - Sensitivity Analysis Based on Source of Participants	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Population-Based	1	94	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.27, 12.53]
12.2 Tertiary Care	2	100	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.56, 7.28]
13 Preterm Delivery - Sensitivity Analysis Including Only Women in Remission at Conception	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Low Birth Weight	1	19	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.08, 4.83]
14.1 Crohn's Disease	1	13	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.03, 13.60]
14.2 Ulcerative Colitis	1	6	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.03, 9.73]
15 Small for Gestational Age	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Any surgery versus no surgery, Outcome 1 Infertility at 12 Months.

Analysis 1.2. Comparison 1 Any surgery versus no surgery, Outcome 2 Infertility at 24 Months.

Analysis 1.3. Comparison 1 Any surgery versus no surgery, Outcome 3 Miscarriage.

Analysis 1.4. Comparison 1 Any surgery versus no surgery, Outcome 4 Miscarriage - Sensitivity Analysis Based on Source of Participants.

Analysis 1.5. Comparison 1 Any surgery versus no surgery, Outcome 5 Miscarriage - Sensitivity Analysis Including Only Women in Remission at Conception.

Analysis 1.6. Comparison 1 Any surgery versus no surgery, Outcome 6 Stillbirth.

Analysis 1.7. Comparison 1 Any surgery versus no surgery, Outcome 7 Stillbirth - Sensitivity Analysis Based on Source of Participants.

Analysis 1.8. Comparison 1 Any surgery versus no surgery, Outcome 8 Stillbirth - Sensitivity Analysis Including Only Women in Remission at Conception.

Study or subgroup	Surgery n/N	No surgery n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=0.15(P=0.88)					
Favours surgery 0.01 0.1 1 10 100 Favours no surgery					

Analysis 1.9. Comparison 1 Any surgery versus no surgery, Outcome 9 Use of ART.

Study or subgroup	Surgery n/N	No surgery n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Johnson 2004	20/66	0/40			25.09[1.56,403.76]
Favours no surgery 0.01 0.1 1 10 100 Favours surgery					

Analysis 1.10. Comparison 1 Any surgery versus no surgery, Outcome 10 Caesarean Section.

Study or subgroup	Surgery n/N	No surgery n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Crohn's Disease					
Zavorova 2017	4/5	2/9		37.8%	3.6[0.98,13.19]
Subtotal (95% CI)	5	9		37.8%	3.6[0.98,13.19]
Total events: 4 (Surgery), 2 (No surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.93(P=0.05)					
1.10.2 Ulcerative Colitis					
Zavorova 2017	2/2	2/4		62.2%	1.67[0.61,4.59]
Subtotal (95% CI)	2	4		62.2%	1.67[0.61,4.59]
Total events: 2 (Surgery), 2 (No surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.99(P=0.32)					
Total (95% CI)	7	13		100%	2.23[1.4,95]
Total events: 6 (Surgery), 4 (No surgery)					
Heterogeneity: Tau ² =0; Chi ² =0.92, df=1(P=0.34); I ² =0%					
Test for overall effect: Z=1.97(P=0.05)					
Test for subgroup differences: Chi ² =0.84, df=1 (P=0.36), I ² =0%					
Favours surgery 0.01 0.1 1 10 100 Favours no surgery					

Analysis 1.11. Comparison 1 Any surgery versus no surgery, Outcome 11 Preterm Delivery.

Study or subgroup	Surgery n/N	No surgery n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Crohn's Disease					
Hudson 1997	2/33	2/61		30.35%	1.85[0.27,12.53]
Nielsen 1984	13/57	2/23		56.09%	2.62[0.64,10.72]
Zavorova 2017	0/5	0/9			Not estimable
Subtotal (95% CI)	95	93		86.44%	2.32[0.75,7.21]
Favours surgery 0.01 0.1 1 10 100 Favours no surgery

Analysis 1.12. Comparison 1 Any surgery versus no surgery, Outcome 12 Preterm Delivery - Sensitivity Analysis Based on Source of Participants.

Analysis 1.13. Comparison 1 Any surgery versus no surgery, Outcome 13 Preterm Delivery - Sensitivity Analysis Including Only Women in Remission at Conception.

Analysis 1.14. Comparison 1 Any surgery versus no surgery, Outcome 14 Low Birth Weight.

Analysis 1.15. Comparison 1 Any surgery versus no surgery, Outcome 15 Small for Gestational Age.

Comparison 2. Laparoscopic versus open surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infertility at 12 Months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Laparoscopic versus open surgery, Outcome 1 Infertility at 12 Months.

ADDITIONAL TABLES

Table 1. Sample size and outcomes among studies included in the meta-analysis

				In-fer-tility	Secondary outcomes						
Study	Comparison	Type of IBD	Total sample size	12 months	24 months	Miscarriage	Still-birth	Use of Caesarean section	Preterm delivery	Low birth weight	Small for gestational age
Banks 1957	Any previous surgery vs no previous surgery	UC	56 women (87 pregnancies)			87 pregnancies	72 pregnancies				
Bartels 2012	Open vs laparoscopic IPAA	UC	37 women	37 women							
Bortoli 2011	Any previous surgery vs no previous surgery	CD	145 women			145 women					
Hudson 1997	Any previous surgery vs no previous surgery	CD	86 women ^a			86 women					
		UC	104 women ^a			104 pregnancies ^a	94 pregnancies		94 pregnancies		
Johnson 2004	IPAA vs no previous surgery	UC	106 women ^a	106 women ^a				106 women			
Koivusalo 2009	Restorative proctocolectomy with ileoanal anastomosis vs no previous surgery	UC	8 women ^a	8 women ^a							
Moser 2000	Any previous surgery vs no previous surgery	CD	65 women (76 pregnancies)								65 pregnancies

Table 1. Sample size and outcomes among studies included in the meta-analysis (Continued)

				nan- cies ^b			
Naganuma 2011	Any previous surgery vs no previous surgery	CD	80 women (69 pregnancies ^c)	69 preg- nancies ^d			
		UC	245 women (234 pregnan- cies ^c)	234 pregnan- cies ^d			
Nielsen 1984	Any previous surgery vs no previous surgery	CD	68 women (109 pregnan- cies)	109 pregnan- cies	80 preg- nan- cies	80 preg- nan- cies	
Zavorova 2017	Any previous surgery vs no previous surgery	CD	12 women (14 pregnancies)		14 preg- nan- cies	14 preg- nan- cies	13 preg- nan- cies ^e
	IPAA vs no previous surgery	UC	5 women (6 pregnancies)		6 preg- nan- cies	6 preg- nan- cies	6 preg- nan- cies

^aExcludes women who were voluntarily infertile or were excluded from estimates of infertility for other reasons (e.g. not married or cohabitating).

^bFor women with multiple pregnancies, one was chosen at random.

^cOnly pregnancies occurring on or after the onset of IBD were included.

^dPregnancies among women with CD and UC were analyzed together.

^eBirthweight was missing for one infant

ART: assisted reproductive technology.

CD: Crohn's disease.

IBD: inflammatory bowel disease.

UC: ulcerative colitis.

Table 2. Sample size and outcomes among studies comparing women before and after surgery

			Infertility				Secondary outcomes				
Study	Type of surgery	Type of sample IBD	Total sample	6 months	12 months	24 months	Miscarriage	Stillbirth	Use of ART	Caesarean section	Time to pregnancy

Table 2. Sample size and outcomes among studies comparing women before and after surgery (Continued)

Gorgun 2004	Restorative proctocolectomy with IPAA	UC 185 women	Before: 117 women After: 120 women Both before and after: 52 women	Before: 45 women ^a After: 70 women ^a
Hahnloser 2004	IPAA	UC 37 women	Before and after: 37 women (37 pregnancies)	Before: 27 women (27 pregnancies) After: 31 women (31 pregnancies)
Johnson 2004	IPAA	UC 153 women	Before: 95 women ^a After: 66 women ^a	Before: 95 women ^a After: 66 women ^a
Mortier 2006	Total colectomy with ileorectal anastomosis	UC 37 women	Before: Before: 5 women ^a After: 15 women ^a After: 15 women ^a	Before: 5 women ^a After: 5 women ^a
Olsen 2002	Restorative proctocolectomy with IPAA	UC 290 women (331 attempted pregnancies)	Before: 84 attempted pregnancies ^a After: 149 attempted pregnancies ^a	Before: 84 attempted pregnancies ^a After:

Table 2. Sample size and outcomes among studies comparing women before and after surgery (Continued)

				149 at-tempted pregnancies ^a				
Ravid 2002	IPAA	UC 38 women ^b			Before: 12 women (16 pregnancies) After: 38 women (65 pregnancies ^c)	Before: 11 pregnancies After: 49 pregnancies ^c	Before: 11 pregnancies After: 48 pregnancies (49 deliveries ^d)	
Tulchinsky 2013	Restorative proctocolectomy	UC 41 women	Before: 26 women ^a After: 27 women ^a		Before: 26 women (70 pregnancies) After: 17 women (32 pregnancies)	Before: 26 women (70 pregnancies) ^a After: 27 women (32 pregnancies) ^a	Before: 62 pregnancies After: 26 pregnancies	Before: 26 women (70 pregnancies) After: 17 women (32 pregnancies)

^aUnclear how many women were at risk of developing the outcome both before and after surgery.

^bAll women included in the study gave birth at least once after IPAA.

^cOngoing pregnancies excluded at the time of the study.

^dA set of twins included (one born vaginally and one born via Caesarean section).

ART: assisted reproductive technology.

CD: Crohn's disease.

IBD: inflammatory bowel disease.

IPAA: ileal pouch anal anastomosis.

UC: ulcerative colitis.

Table 3. Infertility at 12 months in female patients with UC before and after surgery

Type of surgery	Study	Before surgery		After surgery	
		Infertile, n (%)	Total, n	Infertile, n (%)	Total, n
Restorative proctocolectomy with IPAA	Gorgun 2004	45 (38.5)	117	70 (58.3)	120
	Olsen 2002	18 (21.4)	84	122 (81.9)	149
IPAA	Johnson 2004	4 (4.2)	95	29 (43.9)	66
Total colectomy with ileorectal anastomosis	Mortier 2006	1 (20.0)	5	8 (53.3)	15
Restorative proctocolectomy	Tulchinsky 2013	0 (0.0)	26	10 (37.0)	27
Total		68 (20.8)	327	239 (63.4)	377

IPAA: ileal pouch anal anastomosis.

Table 4. Infertility at 12 months in female patients with UC before and after surgery as reported in Gorgun 2004

Age at surgery	Before surgery		After surgery	
	Infertile, n (%)	Total, n	Infertile, n (%)	Total, n
≤ 19 years	0 (0)	1	4 (50)	8
20 to 34 years	38 (40.9)	93	61 (57.0)	107
≥ 35 years	7 (30.4)	23	5 (100)	5

UC: ulcerative colitis.

Table 5. Infertility at 24 months in female patients with UC before and after surgery

Type of surgery	Study	Before surgery		After surgery	
		Infertile, n (%)	Total, n	Infertile, n (%)	Total, n
Restorative proctocolectomy with IPAA	Olsen 2002	13 (15.5)	84	108 (72.5)	149
Restorative proctocolectomy	Mortier 2006	1 (20.0)	5	7 (46.7)	15
Total		14 (15.7)	89	115 (70.1)	164

IPAA: ileal pouch anal anastomosis.

UC: ulcerative colitis.

Table 6. Miscarriage in female patients with UC before and after surgery

Type of surgery	Study	Before surgery		After surgery	
		Miscarriage, n (%)	Total, n	Miscarriage, n (%)	Total, n
IPAA	Hahnloser 2004	10 (27.0)	37	6 (16.2)	37
	Ravid 2002	1 (6.3)	16	9 (13.8)	65
Restorative procto-colectomy	Tulchinsky 2013	8 (11.4)	70	6 (18.8)	32
Total		19 (15.4)	123	21 (15.7)	134

IPAA: ileal pouch anal anastomosis.

UC: ulcerative colitis.

Table 7. Stillbirth in female patients with UC before and after surgery

Type of surgery	Study	Before surgery		After surgery	
		Stillbirth, n (%)	Total, n	Stillbirth, n (%)	Total, n
IPAA	Hahnloser 2004	2 (7.4)	27	2 (6.5)	31
Restorative proctocolectomy	Ravid 2002	0 (0)	11	1 (2.0)	49
Total		2 (5.3)	38	3 (3.8)	80

IPAA: ileal pouch anal anastomosis.

UC: ulcerative colitis.

Table 8. Use of ART in female patients with UC 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	5 (5.3)	95 ^a	20 (30.3)	66 ^a
Restorative proctocolectomy with IPAA	Gorgun 2004	19 (42.2)	45 ^b	36 (51.4)	70 ^b
Restorative proctocolectomy	Tulchinsky 2013	6 (8.6)	70 ^c	11 (34.3)	32 ^c

^aNumbers of women attempting pregnancy before and after surgery.

^bNumber of women infertile following 12 months of attempting pregnancy.

^cNumber of pregnancies in which women used ART.

Note: Totals not calculated due to differing denominators among included studies.

ART: assisted reproductive technology.

IPAA: ileal pouch anal anastomosis.

UC: ulcerative colitis.

Table 9. Caesarean section in female patients with UC before and after surgery

Type of surgery	Study	Before surgery		After surgery	
		Caesarean section, n (%)	Total, n	Caesarean section, n (%)	Total, n
IPAA	Ravid 2002	0 (0)	11	24 (49.0)	49 ^a
Restorative proctocolectomy	Tulchinsky 2013	8 (12.9)	62	12 (46.2)	26
Total		8 (11.0)	73	36 (48.0)	75

^aIncludes a set of twins (one born vaginally and one born via Caesarean section).

IPAA: ileal pouch anal anastomosis.

UC: ulcerative colitis.

Table 10. Time to pregnancy in female patients with UC before and after surgery, measured in months

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

^aPregnancy occurred "immediately" in 32 pregnancies.

^b17/27 women successfully conceived.

SD: standard deviation.

UC: ulcerative colitis.

APPENDICES

Appendix 1. Search strategy

MEDLINE

1 exp Inflammatory Bowel Diseases/

2 exp Colitis, Ulcerative/

3 exp Crohn Disease/

4 exp Proctitis/

5 crohn*.mp.

6 (ulcerative adj colitis).mp.

7 "inflammatory bowel disease*".mp.

8 IBD.mp.

9 or/1-8

- 10 exp Colectomy/
- 11 exp Colonic Pouches/
- 12 exp Enterostomy/
- 13 exp Fibrin Tissue Adhesive/
- 14 (bowel adj resect*).mp.
- 15 (intestin* adj resect*).mp.
- 16 strictur?plast*.mp.
- 17 colectom*.mp.
- 18 proctocolectom*.mp.
- 19 proctectom*.mp.
- 20 ileostom*.mp.
- 21 anastomo*.mp.
- 22 IPAA.mp.
- 23 (J adj pouch*).mp.
- 24 fistulotom*.mp.
- 25 seton*.mp.
- 26 (fibrin adj glue).mp.
- 27 or/10-26
- 28 exp Fertility/
- 29 Infertility/
- 30 Infertility, Female/
- 31 exp Pregnancy/
- 32 exp Pregnancy Rate/
- 33 Fertility Agents/
- 34 Fertility Agents, Female/
- 35 exp Reproductive Techniques, Assisted/
- 36 exp Pregnancy Complications/
- 37 exp Obstetric Labor, Premature/
- 38 exp Infant, Low Birth Weight/
- 39 exp Intensive Care, Neonatal/
- 40 exp Infant, Premature/
- 41 exp Cesarean Section/
- 42 exp Extraction, Obstetrical/
- 43 pregnan*.mp.
- 44 stillbirth*.mp.

- 45 miscarri*.mp.
- 46 implant*.mp.
- 47 embryo*.mp.
- 48 tubal abort*.mp.
- 49 (spontaneous* adj5 abort*).mp.
- 50 ((fet* or foet* or intrauterine*) adj5 (death or loss)).mp.
- 51 fecundity.mp.
- 52 fertilit*.mp.
- 53 subfertil*.mp.
- 54 infertil*.mp.
- 55 (assist* adj5 reproduct*).mp.
- 56 c?sarean section.mp.
- 57 "low birth weight".mp.
- 58 ((prematur* or immatur*) adj5 lab*r).mp.
- 59 (small adj5 (gestation* adj5 age)).mp.
- 60 forceps.mp.
- 61 vacuum.mp.
- 62 "neonatal intensive care".mp.
- 63 (infant* adj5 resuscitat*).mp.
- 64 Postpartum Hemorrhage/
- 65 ((postpart* or puerperal or ante*) adj5 h?morrhage).mp.
- 66 exp Diabetes, Gestational/
- 67 ((gestation* or matern* or pregnan*) adj5 diabet*).mp.
- 68 exp Hypertension, Pregnancy-Induced/
- 69 ((gestation* or matern* or pregnan*) adj5 hypertensi*).mp.
- 70 preeclamps*.mp.
- 71 eclampsi*.mp.
- 72 Placenta, Retained/
- 73 ((retain* or retention) adj5 placenta*).mp.
- 74 exp Depression, Postpartum/
- 75 ((postpart* or puerperal or maternal or puerperium) adj5 depress*).mp.
- 76 (time adj5 (pregnancy or conception)).mp.
- 77 (fertility adj5 rate*).mp.
- 78 or/28-77
- 79 9 and 27 and 78

Embase

- 1 exp Inflammatory Bowel Disease/
- 2 exp Ulcerative Colitis/
- 3 exp Crohn Disease/
- 4 exp Proctitis/
- 5 exp Pancolitis/
- 6 exp Proctocolitis/
- 7 crohn*.mp.
- 8 (ulcerative adj colitis).mp.
- 9 "inflammatory bowel disease*".mp.
- 10 IBD.mp.
- 11 or/1-10
- 12 exp Gastrointestinal Surgery/
- 13 exp Fibrin Glue/
- 14 (bowel adj resect*).mp.
- 15 (intestin* adj resect*).mp.
- 16 strictur?plast*.mp.
- 17 colectom*.mp.
- 18 proctocolectom*.mp.
- 19 proctectom*.mp.
- 20 ileostom*.mp.
- 21 anastomo*.mp.
- 22 IPAA.mp.
- 23 (J adj pouch*).mp.
- 24 fistulotom*.mp.
- 25 seton*.mp.
- 26 (fibrin adj glue).mp.
- 27 or/12-26
- 28 exp Fertility/
- 29 exp Infertility/
- 30 exp Infertility therapy/
- 31 exp Pregnancy/
- 32 exp Pregnancy Rate/
- 33 exp Pregnancy Complication/
- 34 exp Spontaneous Abortion/

- 35 exp Fetus Death/
- 36 exp Instrumental Delivery/
- 37 exp "Immature and Premature Labor"/
- 38 exp Low Birth Weight/
- 39 exp Newborn Intensive Care/
- 40 exp Fetal Extraction Device/
- 41 pregnan*.mp.
- 42 stillbirth*.mp.
- 43 miscarri*.mp.
- 44 implant*.mp.
- 45 embryo*.mp.
- 46 tubal abort*.mp.
- 47 (spontaneous* adj5 abort*).mp.
- 48 ((fet* or foet* or intrauterine*) adj5 (death or loss)).mp.
- 49 fecundity.mp.
- 50 fertilit*.mp.
- 51 subfertil*.mp.
- 52 infertil*.mp.
- 53 (assist* adj5 reproduct*).mp.
- 54 c?sarean section.mp.
- 55 "low birth weight".mp.
- 56 ((prematur* or immatur*) adj5 lab*r).mp.
- 57 (small adj5 (gestation* adj5 age)).mp.
- 58 forceps.mp.
- 59 vacuum.mp.
- 60 "neonatal intensive care".mp.
- 61 (infant* adj5 resuscitat*).mp.
- 62 exp Obstetric Hemorrhage/
- 63 ((postpart* or puerperal or ante*) adj5 h?morrhage).mp.
- 64 exp pregnancy diabetes mellitus/
- 65 ((gestation* or matern* or pregnan*) adj5 diabet*).mp.
- 66 exp Maternal Hypertension/
- 67 ((gestation* or matern* or pregnan*) adj5 hypertensi*).mp.
- 68 exp Eclampsia/
- 69 exp Preeclampsia/

70 preeclampsia*.mp.
71 eclampsia*.mp.
72 retained placenta/
73 ((retain* or retention) adj5 placenta*).mp.
74 exp Puerperal Depression/
75 ((postpart* or puerperal or maternal or puerperium) adj5 depress*).mp.
76 (time adj5 (pregnancy or conception)).mp.
77 (fertility adj5 rate*).mp.
78 or/28-77
79 11 and 27 and 78
80 limit 79 to conference abstract
81 79 not 80

CENTRAL

1 exp Inflammatory Bowel Diseases/
2 exp Colitis, Ulcerative/
3 exp Crohn Disease/
4 exp Proctitis/
5 crohn*.mp.
6 (ulcerative adj colitis).mp.
7 "inflammatory bowel disease*".mp.
8 IBD.mp.
9 or/1-8
10 exp Colectomy/
11 exp Colonic Pouches/
12 exp Enterostomy/
13 exp Fibrin Tissue Adhesive/
14 (bowel adj resect*).mp.
15 (intestin* adj resect*).mp.
16 strictur?plast*.mp.
17 colectom*.mp.
18 proctocolectom*.mp.
19 proctectom*.mp.
20 ileostom*.mp.
21 anastomo*.mp.
22 IPAA.mp.

- 23 (J adj pouch*).mp.
- 24 fistulotom*.mp.
- 25 seton*.mp.
- 26 (fibrin adj glue).mp.
- 27 or/10-26
- 28 exp Fertility/
- 29 Infertility/
- 30 Infertility, Female/
- 31 exp Pregnancy/
- 32 exp Pregnancy Rate/
- 33 Fertility Agents/
- 34 Fertility Agents, Female/
- 35 exp Reproductive Techniques, Assisted/
- 36 exp Pregnancy Complications/
- 37 exp Obstetric Labor, Premature/
- 38 exp Infant, Low Birth Weight/
- 39 exp Intensive Care, Neonatal/
- 40 exp Infant, Premature/
- 41 exp Cesarean Section/
- 42 exp Extraction, Obstetrical/
- 43 pregnan*.mp.
- 44 stillbirth*.mp.
- 45 miscarri*.mp.
- 46 implant*.mp.
- 47 embryo*.mp.
- 48 tubal abort*.mp.
- 49 (spontaneous* adj5 abort*).mp.
- 50 ((fet* or foet* or intrauterine*) adj5 (death or loss)).mp.
- 51 fecundity.mp.
- 52 fertilit*.mp.
- 53 subfertil*.mp.
- 54 infertil*.mp.
- 55 (assist* adj5 reproduct*).mp.
- 56 c?sarean section.mp.
- 57 "low birth weight".mp.

58 ((premat* or immatur*) adj5 lab*r).mp.
59 (small adj5 (gestation* adj5 age)).mp.
60 forceps.mp.
61 vacuum.mp.
62 "neonatal intensive care".mp.
63 (infant* adj5 resuscitat*).mp.
64 Postpartum Hemorrhage/
65 exp Diabetes, Gestational/
66 exp Hypertension, Pregnancy-Induced/
67 exp Placenta, Retained/
68 exp Depression, Postpartum/
69 ((postpart* or puerperal or ante*) adj5 h?morrhage).mp.
70 ((gestation* or matern* or pregnan*) adj5 diabet*).mp.
71 ((gestation* or matern* or pregnan*) adj5 hypertensi*).mp.
72 preeclamps*.mp.
73 eclamps*.mp.
74 ((retain* or retention) adj5 placenta*).mp.
75 ((postpart* or puerperal or maternal or puerperium) adj5 depress*).mp.
76 (time adj5 (pregnancy or conception)).mp.
77 (fertility adj5 rate*).mp.
78 or/28-77
79 9 and 27 and 78

Cochrane IBD Group Specialized Register

Keyword/abstract search: Surgical therapies and fertility

IBD and female fertility

Inflammatory Bowel Disease and female fertility

CONTRIBUTIONS OF AUTHORS

Designing the review: MC, SL, CHS, GKG, AM, EIB, MEK.

Coordinating the review: CHS, EIB, MEK.

Developing the search strategy: MC, CHS, EIB, MEK.

Collecting data: SL, MC.

Performing the literature search: MC, MEK.

Selecting papers for full review: SL, MC, CHS, EIB, MEK.

Obtaining papers for review: MC, MEK.

Screening papers for inclusion in the review: SL, MC, CHS, EIB, MEK.

Assessing the quality of papers: SL, MC.

Extracting data from papers: SL, MC.

Managing data: SL, MC, MEK.

Entering data into RevMan software: SL, MC.

Analyzing data: SL, MC, MEK.

Interpreting data: SL, MC, CHS, PGK, GGK, AM, AR, EIB, MEK.

Providing a methodological perspective: CHS, PGK, GGK, AM, AR, EIB, MEK.

Writing the review: SL, MC, CHS, MEK, EIB.

Critically revising the manuscript: SL, MC, CHS, PGK, GGK, AM, AR, EIB, MEK.

EIB and MEK made equal contributions to this manuscript and are both senior authors.

DECLARATIONS OF INTEREST

Sangmin Lee: none known.

Megan Crowe: none known.

Cynthia H Seow: Dr. Seow 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. Dr. Seow has also provided lectures for Janssen Pharmaceuticals, Abbvie, Ferring, Shire, and Takeda.

Paulo G. Kotze: Dr. Kotze has received speaking and consultancy honoraria from Abbvie, Janssen, Pfizer, Takeda, and UCB.

Gilaad G Kaplan: Dr. Kaplan 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.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We present here some noteworthy differences between the published protocol and the review. First, we added a comparison of any surgery to no surgery, as this was the comparison presented in most of the studies identified in our search (see [Types of interventions](#)). These studies provided insufficient detail to differentiate between small bowel resection, ileocecal resection, colectomy, IPAA, and strictureplasty. Second, we added an additional sensitivity analysis excluding pregnancies among women with active disease at conception or diagnosed with IBD during pregnancy or in the postpartum period. Third, we were not able to conduct several of our planned subgroup and sensitivity analyses (see [Subgroup analysis and investigation of heterogeneity](#) and [Sensitivity analysis](#)) including the following:

- Subgroup analyses of surgeries that were conducted with and without the use of adhesion barrier agents;
- Subgroup analyses based on extent of UC;
- Subgroup analyses based on disease behavior of CD;
- Sensitivity analyses excluding all studies with an overall high risk of bias;
- Excluding studies published only as an abstract;
- Limiting analyses to randomized studies; and
- Limiting analyses to women who had a viable pregnancy before undergoing surgery for management of their IBD.

Last, some studies reported only adjusted ORs and 95% CIs. When this was the case for ≥ 1 of the studies included in the meta-analysis for a given outcome, we used the generic inverse variance method to calculate a pooled OR.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Rate; *Proctocolectomy, Restorative [adverse effects]; Colonic Pouches [adverse effects]; Infertility, Female [epidemiology] [*etiology]; Inflammatory Bowel Diseases [*surgery]; Postoperative Complications [epidemiology]; Pregnancy Outcome; Randomized Controlled Trials as Topic; Reproductive Techniques, Assisted

MeSH check words

Female; Humans; Pregnancy