



Published in final edited form as:

Contraception. 2025 November ; 151: 111038. doi:10.1016/j.contraception.2025.111038.

Contraceptive use among women with inflammatory bowel disease: An updated systematic review

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Abstract

Background: Hormonal contraceptive use by women with inflammatory bowel disease (IBD) might affect risk of adverse outcomes or contraceptive effectiveness. Our objective was to update a previous systematic review on the safety and effectiveness of contraceptive use among women with IBD.

Methods: We searched multiple databases from inception through July 15, 2024 for articles on contraception and IBD. Outcomes were IBD disease activity or relapse, other adverse health outcomes, and oral contraceptive (OC) effectiveness. We assessed risk of bias for each study and certainty of evidence for most outcomes.

Results: Fifteen articles met our inclusion criteria; 8 were new. Twelve had high risk of bias and three moderate risk. One cohort study found lower odds of IBD symptoms among hormonal contraceptive users compared with non-hormonal users, but higher odds of intestinal inflammation over one year. Nine cohort studies found inconsistent results regarding OC use and disease activity or relapse, with increased and decreased associations; most were not statistically significant. Two cohort studies found no statistically significant associations between OC use and VTE among IBD patients. One study found no statistically significant association between OC use and abnormal cervical smears. Two pharmacokinetic studies suggested no differences in plasma concentrations of steroid hormones after oral ingestion among participants with and without IBD. We found no evidence examining risk of osteoporosis or osteopenia among women with IBD using contraception.

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Competing interests: The authors declare that they have no competing interests.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Oak Ridge Institute for Science and Education.

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Conclusions: Limited evidence suggested inconsistent findings for increased risk of disease activity or relapse among women with IBD using hormonal contraception (very low certainty of evidence), no differences in other adverse events (very low certainty of evidence), and no differences in contraceptive hormone concentrations.

Keywords

contraception; inflammatory bowel disease; relapse; venous thromboembolism; contraceptive effectiveness; systematic review

1. Introduction

Inflammatory bowel disease (IBD) is comprised of two gastrointestinal disorders—ulcerative colitis and Crohn’s disease—which have distinct clinical and pathological features. Ulcerative colitis is characterized by relapsing and remitting episodes of inflammation limited to the superficial mucosal layer of the large bowel (colon or rectum), whereas Crohn’s disease is characterized by inflammation throughout the bowel layers and may involve any segment of the gastrointestinal tract from oral cavity to anus [1]. Common symptoms of both disorders include diarrhea, rectal bleeding, frequent bowel movements, weight loss, fatigue, and anemia [2,3]. Through clinical evaluation, endoscopy, imaging, and biopsy, clinicians can usually differentiate between ulcerative colitis and Crohn’s disease [4]. IBD often presents during the reproductive years. The peak age of incidence of Crohn’s disease is during the third decade of life, with decreasing incidence afterward, and the incidence of ulcerative colitis is stable between the third and seventh decades [2]. Globally, 59 per 100,000 individuals had IBD in 2019, with variation by country, and slightly higher prevalence among women than men [5].

Although the etiology of IBD remains unknown, genetic and environmental factors are thought to contribute to its development. One risk factor for onset of disease includes oral contraceptive (OC) use, with stronger evidence of an association in studies published before compared with after 2000, possibly because of different OC doses [6,7]. The mechanism through which OC use influences development of IBD is not known, however proposed theories include effects of exogenous estrogen on immunomodulation, intestinal wall function, gut microbiome, and hypercoagulability [8]. Since OC use is considered a risk factor for disease onset, it is reasonable to consider that OC use among women with IBD might result in exacerbation of symptoms or disease relapse.

Individuals with IBD have a two-fold increased risk for venous thromboembolism (VTE) compared with unaffected individuals [9]. Risk factors for VTE among patients with IBD include active disease, steroid therapy, disease subtype, greater age, and surgery [10,11]. While the cause of VTE among IBD patients is uncertain, underlying mechanisms might be the inflammatory process, fluid depletion, vitamin deficiencies, and prolonged immobilization [12]. Given that IBD patients are at increased risk of VTE, there are concerns that use of combined hormonal contraceptives and depot medroxyprogesterone acetate (DMPA) which are known to increase VTE risk [13–16] might compound the risk.

Patients with IBD might have a higher prevalence of osteoporosis and osteopenia than the general population [17]. The use of DMPA has been associated with small and generally reversible changes in bone mineral density [18] and therefore might be of concern in patients who may have other risk factors for adverse effects on bone health.

IBD is also associated with several hepatobiliary disorders, including primary sclerosing cholangitis [19], a chronic cholestatic liver disease that leads to progressive cirrhosis and ultimately hepatic failure. Since hormonal contraceptives are metabolized by the liver, their use might adversely affect a woman with IBD and whose liver function is severely compromised.

Factors that may impair absorption of OC sex steroids might impact contraceptive effectiveness. These include inflammation and ulceration of the intestinal mucosa, and more rapid transit of gastrointestinal contents in patients who have undergone bowel surgery [20]. Since most absorption of OC steroids occurs in the small bowel [20], OC malabsorption is unlikely to occur among women with only large bowel disease, such as ulcerative colitis, unless surgical treatment in these women involves the small bowel. There are concerns that IBD-related malabsorption might decrease the efficacy of orally-ingested contraceptives [21].

A systematic review published in 2010 identified 10 studies examining contraceptive use among women with IBD and found no increased risk of disease relapse among women with IBD who used OCs compared with women not using OCs, and no differences in the absorption of higher dose combined OCs (COCs) among women with mild ulcerative colitis and small ileal resections compared with healthy women [22]. The current review aims to update the body of evidence on the safety and effectiveness of specific contraceptive methods among women with IBD. The information may be used by guideline development groups that publish evidence-based contraception guidance for clinicians and patients. We focused on two research questions:

1. Among women with IBD, does use of a specific contraceptive method increase the risk of IBD relapse or other adverse health outcomes (e.g., VTE, osteopenia/osteoporosis, hepatobiliary disorder) compared with no use of contraception or use of a different specific contraceptive method?
2. Among women using OCs, does having IBD modify contraceptive effectiveness (e.g., pregnancy or proxy measures of pregnancy risk, such as ovulation, exogenous [contraceptive] hormone levels) compared with not having IBD?

2. Materials and Methods

We conducted this systemic review according to an a priori protocol, which has been registered in the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42024507789(23) and reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses [24].

2.1 Eligibility criteria

Studies were eligible for inclusion if they examined outcomes occurring after IBD diagnosis among women using a contraceptive method at or after diagnosis with IBD. We excluded studies that examined the risk of developing IBD among women using contraception.

For our first research question (among women with IBD, does use of a specific contraceptive method increase the risk of IBD relapse or other adverse health outcomes compared with no use of contraception or use of a different specific contraceptive method), the population of interest was women of reproductive age (e.g., aged 15–49 years, although age ranges differed in individual studies based on study inclusion criteria) with IBD. The exposure of interest was current use of any contraceptive method, including COCs, combined injectable contraceptives, contraceptive patch, contraceptive ring, progestin-only pills, progestin-only injectables, progestin-only implants, levonorgestrel-releasing IUDs, copper IUDs, barrier methods, permanent contraception, fertility awareness-based methods, withdrawal, lactational amenorrhea method, and emergency contraception. The comparison was no use of contraception, or use of a different specific contraceptive method than the exposure contraceptive method. Outcomes of interest were IBD disease activity or relapse (e.g., need for surgery, time to relapse) and other adverse health outcomes or events (e.g., VTE, osteoporosis or osteopenia).

For our second research question (among women using OCs, does having IBD modify contraceptive effectiveness compared with not having IBD), the population of interest was women of reproductive age using OCs (combined or progestin-only). The exposure of interest was diagnosis of IBD, and the comparison was no diagnosis of IBD. The outcome of interest was contraceptive effectiveness (i.e., pregnancy, proxy measures of pregnancy risk such as ovulation or hormone plasma concentration levels).

We included randomized trials, non-randomized trials, cohort studies, case-control studies, and cross-sectional studies that included a retrospective analysis of change in outcomes over time. We excluded non-comparative studies such as case reports and case series. All settings (e.g., hospital, clinic, or community) and all countries were considered.

2.2 Literature search

We worked with a research librarian at the US Centers for Disease Control and Prevention to develop a comprehensive search strategy modeled after the strategy from the previous review [22] (Supplementary Material 1). We searched for studies relevant to contraceptive use (all methods) and IBD. The search was conducted in MEDLINE, EMBASE, Global Health, Cochrane Library, CINAHL, Scopus, [ClinicalTrials.gov](https://www.clinicaltrials.gov), and WHO ICTRP databases from database inception through July 15, 2024. We also reviewed references in systematic reviews and key review articles to optimize our search. We considered articles in all languages. We did not consider abstracts without full text articles.

2.3 Study selection and data extraction

Among articles identified by the search strategy, all titles and abstracts were screened independently by at least two co-authors, using the Covidence platform [25]. Two co-authors

then reviewed full-text articles to determine if they met inclusion criteria. Any conflicts were resolved by co-author discussion. We used standardized evidence tables to summarize information on each included study.

2.4 Risk of bias assessment

We assessed risk of bias using a modified version of the Cochrane tool(26) for each included study. We considered selection bias, information bias for exposures and outcomes, and confounding. For each study, we derived a judgement for overall risk of bias based on the ratings for each domain: we considered the study to have an overall low risk of bias if all domains were rated as low risk; we considered the study to have an overall moderate risk of bias if we had some concerns in at least one domain and no domains were rated as high risk; and we considered the study to have an overall high risk of bias if at least one domain was rated as high risk. Two co-authors independently completed the assessments, and any conflicts were resolved by co-author discussion.

2.5 Data synthesis

We summarized descriptive statistics, crude and adjusted point estimates, and results of significance tests. We did not conduct meta-analyses due to heterogeneity of study populations, exposures, outcomes, and lengths of follow-up.

2.6 Certainty of evidence

We assessed the certainty of evidence for all outcomes except those from pharmacokinetic studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [27, 28]. For each eligible outcome, we considered risk of bias, inconsistency, imprecision, and indirectness to be not serious, serious, or very serious. Based on these assessments, the certainty of evidence was rated as high, moderate, low, or very low. At baseline, randomized controlled trials are considered to have high certainty and observational studies are considered to have low certainty; ratings are then adjusted based on the criteria previously listed.

3. Results

We screened 1,835 unduplicated articles identified from our database search, from which 79 articles were identified for full-text review (Figure 1). Among these articles, 64 were excluded (34 wrong study design, 12 wrong intervention, 7 wrong outcomes, 5 wrong patient population, 4 wrong comparator, and 2 duplicates). Fifteen studies met inclusion criteria [29–43]; seven [30, 31, 33, 39, 41–43] of these were included in the previous systematic review [22] and eight [29, 32, 34–38, 40] were newly identified. Three articles from the previous review did not meet inclusion criteria for this updated review because they were case reports [44–46].

Four studies assessed participants with IBD overall [29, 32, 37, 38], one of which presented results for ulcerative colitis and Crohn's disease separately [29] and two of which presented multivariable results adjusted for disease type [37, 38]; five studies assessed participants with ulcerative colitis [30, 33, 34, 36, 39], and six studies assessed participants with Crohn's

disease [31, 35, 40–43]. Thirteen articles reported on cohort studies (9 prospective [30–32, 34–36, 40, 42, 43] and 4 retrospective [29, 37, 38, 41]) and 2 reported on pharmacokinetic studies [33, 39]. Of the 13 cohort studies, one assessed hormonal contraceptives as a group [32]; the remaining 10 studies examined OCs [29, 30, 34, 37, 38, 40–43], three of which presented at least some results by OC type (COCs or progestin-only pills [POPs]) [29–31, 34–38, 40–43]. One study also separately examined the progestin IUD [35]. In both pharmacokinetic studies, participants received a single dose of 50 mcg ethinyl estradiol (EE) plus 250 mcg of levonorgestrel (LNG) after an overnight fast [33, 39]. Ten cohort studies assessed the outcome of disease activity or relapse [30–32, 34–36, 40, 41, 43], three cohort studies assessed other adverse health events including VTE and cervical dysplasia [29, 37, 38], and two pharmacokinetic studies assessed changes in contraceptive hormone levels as a proxy for contraceptive effectiveness [33, 39].

3.1 Risk of bias

We assessed the overall risk of bias for each study to be moderate or high (Figure 2). Three studies had overall moderate risk of bias because of the following concerns (but no fatal flaws warranting a high risk judgement): hormonal contraceptive use was prospectively self-reported without validation [32]; the comparison group may have included users of other contraceptive methods that were not specified [35, 36]; or multivariable models were missing important confounders [35, 36]. Twelve studies had high overall risk of bias because of the following concerns considered as fatal flaws: no information on recruitment rates [29, 33, 39, 42, 43]; no information on selection of participants (i.e., inclusion criteria, source population, or time period) to assess similarities or differences between those in the exposed and unexposed groups [33, 39]; no information on attrition [29, 30, 38, 40, 43]; definition and measurement of OC use was not reported [29, 30, 37, 38]; OC use compliance and continuation over follow-up were unknown [31, 34, 40–43]; $\geq 30\%$ of participants had missing data on OC use without reporting on whether those with and without data systematically differed [34, 40]; the comparison group was not defined [29] or may have included current OC users since multivariable models included women with missing OC use data [34] or exposure status was assessed at a single time point and women may have initiated OC use afterwards during follow-up which ranged from 12 months to 10 years [31, 41–43]; outcomes were self-reported without validation [40, 43], the temporality between exposure and outcome was uncertain [40], or crude estimates were reported without adjustment for important confounders [29, 37, 43]. Additionally, these 12 studies with high overall risk of bias had other concerns not considered as fatal flaws: low recruitment rates [34, 37, 41], high attrition [34], the comparison group may have included users of other contraceptive methods that were not specified [30], multivariable models were missing important confounders [30, 31], or crude estimates only were reported, although it is uncertain whether adjustment for confounders was necessary given the outcome [33, 39].

3.2 Research question 1: IBD disease activity or relapse among patients with IBD (Table 1)

3.2.1 Ulcerative colitis: Three studies assessed OC use (type not specified) and risk of disease activity or relapse among participants with ulcerative colitis [30, 34, 36]. All were prospective cohort studies. Specific outcomes included relapse (defined as increase in

symptoms leading to changes in medical treatment or surgery), time to relapse, number of relapses, first ulcerative colitis-related surgery, and first prescriptions for medication (i.e., oral steroids and anti-tumor necrosis factor therapy). Overall, OC use was not associated with statistically significant increases in measures of UC disease activity or relapse, with point estimates above and below 1.0. However, one study that found no overall association between OC use and relapse (rated as having high overall risk of bias) reported statistically significantly greater proportions of OC users compared with never users experienced relapse at 2, 5, and 10 years, and a statistically significant increase in number of relapses during the follow up period (crude hazard ratio [cHR]=1.5; 95% confidence interval [CI]=1.2–1.8) [34].

3.2.2 Crohn's disease: Six studies assessed OC use and risk of disease activity or relapse among participants with Crohn's disease [31, 35, 40–43]; one study examined COCs and POPs analyzed together [31] and five studies did not specify OC type [35, 40–43]. All were prospective cohort studies except one which was a retrospective cohort study [41]. Specific outcomes included relapse (defined differently across studies including increases in Crohn's disease activity index [CDAI], need for surgery, need for repeat surgery), time to relapse, type of attack, CDAI scores during relapse, first Crohn's disease-related surgery, and first prescription for oral steroids. None of the studies reported statistically significant associations between OC use (all types) and any of the outcomes, with point estimates (when reported) less than 2.0. However, one study that found no overall association between OC use and relapse (rated as having moderate overall risk of bias) reported that the risk of surgery increased with duration of COC use ($p=0.041$) but not POP use ($p>0.05$); among COC users, surgery increased by nearly 30% per year of COC use (adjusted hazard ratio [aHR]=1.29, 95% CI=1.05–1.57) [35]. Finally, one study found no association between progestin IUD use and first Crohn's disease-related surgery or first prescription for oral steroids after Crohn's disease diagnosis [35].

3.2.3 Inflammatory bowel disease: Evidence from one cohort study followed women with IBD (ulcerative colitis and Crohn's disease combined) for one year and compared those who used hormonal contraceptives (COCs, POPs, or levonorgestrel [LNG]-IUD) at some point during the year with those who did not [32]. Three IBD-related outcomes were measured: ever having IBD symptoms during follow-up, ever having IBD flares during follow-up, and ever having intestinal inflammation during follow-up. Results indicated lower odds of IBD symptoms (adjusted odds ratio [aOR]=0.16, 95% CI=0.02, 0.90) and flares (aOR=0.53, 95% CI=0.14, 1.93) for hormonal contraceptive users compared with non-users, but higher odds of intestinal inflammation (aOR=5.71, 95% CI= 1.23, 43.63); confidence intervals were wide and not statistically significant for the association with flares.

3.3 Research question 2: Other adverse health outcomes among patients with IBD (Table 2)

3.3.1 Venous thromboembolism (VTE): Two retrospective cohort studies found no statistically significant associations between OC use (definition not provided nor type of OC specified) and risk of VTE among IBD patients [29, 38]. The first study assessed patients with Crohn's disease and ulcerative colitis separately. Among patients with Crohn's disease,

there was a non-significant increased risk of VTE among OC users compared with non-users (crude odds ratio [cOR]=1.53, 95% CI=0.38, 6.2) [29]. No VTE events were observed among OC users with ulcerative colitis. The second study examined IBD patients overall and found a non-significant decreased association between OC use and deep vein thrombosis (aOR=0.57, 95% CI=0.21, 1.53) and a non-significant increased association between OC use and pulmonary embolism (aOR=2.56, 95% CI=0.75, 8.75) [38].

3.3.2 Cervical dysplasia: One retrospective cohort analysis found no association between OC use and having an abnormal cervical smear (low-grade dysplasia, defined as borderline or cervical intraepithelial neoplasia [CIN] I; or high-grade dysplasia, defined as CIN II, CIN III, or higher) after IBD diagnosis compared with non-OC users [37].

3.4 Contraceptive effectiveness among patients using oral contraceptives (Table 3)

No studies were identified that examined pregnancy rates among contraceptive users comparing those with and without IBD. Two studies (both rated as having high overall risk of bias) assessed pharmacokinetic outcomes [33, 39]. One study found that mean bioavailability of ethinyl estradiol (EE) and LNG (single dose 50 mcg EE plus 250 mcg LNG) did not significantly differ ($p>0.10$) between five women with ulcerative colitis and ileostomy involving only the colon (small bowel intact) and five healthy women [33]. The other study assessed LNG levels (single dose 50 mcg EE plus 250 mcg LNG) in healthy controls ($n=5$) and 3 groups of ulcerative colitis patients ($n=15$): group 1 included women with unoperated, mild ulcerative colitis ($n=5$); group 2 included women with proctocolectomy with continent ileostomy ($n=10$, including 4 from group 1); and group 3 included women with conventional ileostomy ($n=5$, including 1 from group 2) [47]. Mean peak LNG levels did not significantly differ among the unoperated patients or the conventional ileostomy patients when compared with controls (p -values not reported), but those with continent ileostomy had significantly lower LNG levels compared with controls ($p<0.05$). For 10-hour LNG levels, values were not significantly different in any of the ulcerative colitis groups with ileostomy compared with controls (p -values not reported); however, those with unoperated ulcerative colitis had higher LNG levels than those in the ileostomy groups ($p<0.01$). No patient with ileostomy went below a 10-hour LNG plasma level previously shown to be sufficient to inhibit ovulation.

3.5 Certainty of evidence

The certainty of evidence was deemed to be very low for all outcomes except for the pharmacokinetic outcomes which were not assessed (Supplementary Material 2-3). For all outcomes, the risk of bias was considered serious or very serious for numerous reasons. For most outcomes, inconsistency could not be assessed because there was only one study examining the outcome; in this situation, overall certainty was rated down one level for inconsistency. For some outcomes, imprecision was considered serious or very serious due to wide CIs that contained both beneficial and harmful effects or no reporting of CIs, wide range or no reporting of other measures of precision, or no reporting of sample size or small total sample size. For all outcomes, indirectness was considered not serious.

4. Discussion

This updated systematic review identified eight new studies examining risk of IBD disease activity or relapse or other adverse health outcomes (i.e., VTE, abnormal cervical smears) among women with IBD using contraception. Of the 15 included studies, one cohort study found lower odds of IBD symptoms among hormonal contraceptive users compared with non-hormonal contraceptive users, but higher odds of intestinal inflammation over one year. Nine cohort studies found inconsistent results regarding OC use and ulcerative colitis or Crohn's disease activity or relapse, with increased and decreased associations for various measures of disease activity or relapse; most were not statistically significant. Two cohort studies found no statistically significant association between OC use and VTE among IBD patients, although confidence intervals were imprecise. One study found no statistically significant association between OC use and abnormal cervical smears. Two pharmacokinetic studies generally suggested no differences in plasma concentrations of steroid hormones after oral ingestion among participants with and without IBD.

Newly identified evidence on IBD disease activity or relapse overall was consistent with evidence included in the previously published systematic review, which concluded no increased risk of disease relapse among women with IBD using OCs [22]. However, the updated evidence base includes two new cohort studies that found significantly increased risk for additional measures of disease activity or relapse comparing OC users with non-users (i.e., number of relapses during follow-up and risk of surgery with longer duration of COC use but not for POP use). The evidence for VTE and abnormal cervical smears is new information. While no association between OC use and abnormal cervical smears was found among women with IBD, we presume that the authors examined the association because some studies have suggested an increased risk of cervical dysplasia among women with IBD [48, 49], and some studies have suggested an increased risk of cervical dysplasia among longer duration OC users [50]. No new evidence was found for contraceptive effectiveness among IBD patients using OCs.

The body of evidence on the safety and effectiveness of contraceptive use among women with IBD has several limitations. Most of the studies were deemed to have high overall risk of bias and the certainty of evidence for all outcomes was rated as very low. Studies that examined VTE had poor generalizability because study populations were not restricted to women of reproductive age. Studies that examined pharmacokinetic outcomes also had poor generalizability because they included small numbers of women with ulcerative colitis, the women had smaller surgical resections limited to the large bowel and findings may not generalize to women with more extensive resections or to women with Crohn's disease with small bowel inflammation, and the doses of steroid hormones used were higher than most OCs used in the United States presently. Few studies examined adverse health outcomes beyond disease activity or relapse, and only one study examined progestin IUD use among women with IBD. We found no evidence examining risk of osteoporosis or osteopenia among women with IBD using contraception was found, nor studies examining hormonal contraception use among women with IBD and compromised liver function. Last, no studies examined pregnancy as a measure of contraceptive effectiveness comparing women with and without IBD.

In conclusion, this updated review expands upon the previous review with eight newly identified studies. However, evidence is still limited in quantity and quality, with inconsistent findings on risk of disease activity or relapse and lack of high-quality evidence on risk of VTE and contraceptive effectiveness. Further research can focus on these gaps to provide information needed by women with IBD as they make contraceptive choices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank Joanna Taliano, MA, MLS, for helping to build the evidence search strategy and running the searches; and Sophia Garbarino for helping to retrieve articles for consideration.

Funding source:

This project was supported in part by an appointment to the Research Participation Program at the Centers for Disease Control and Prevention administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the Centers for Disease Control and Prevention.

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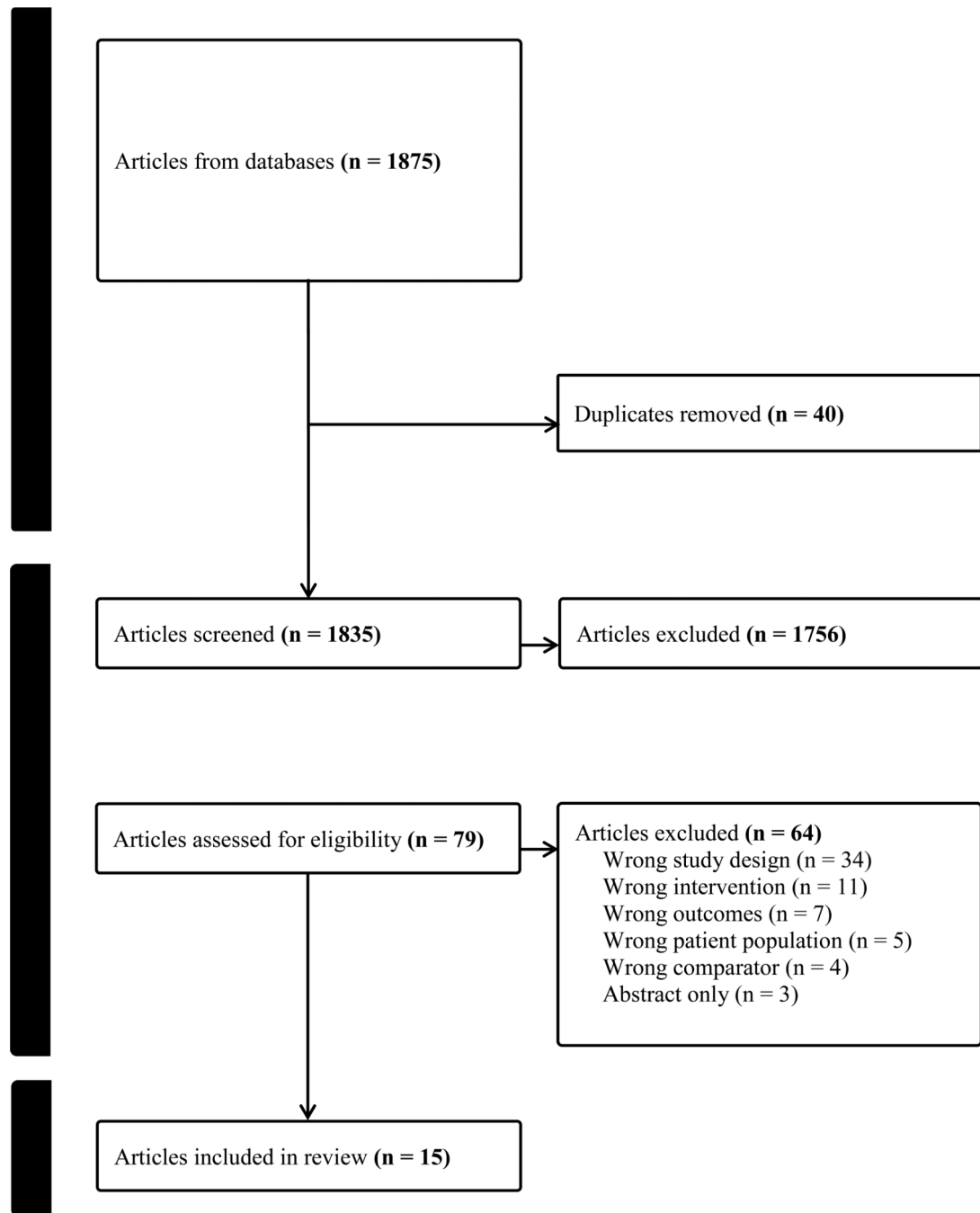


Figure 1. PRISMA flow chart of the search process for evidence on the safety and effectiveness of contraceptive use among women with IBD

Study	Selection bias	Information bias	Confounding bias	Overall risk of bias
<i>Outcome: IBD disease activity or relapse among patients with IBD</i>				
Bitton 2001(30)	-	-	?	-
Cosnes 1999(31)	+	-	?	-
Dolovich 2024(32)	+	?	+	?
Hoie 2007(34)	?	-	+	-
Khalili 2016(35)	+	?	?	?
Khalili 2016(36)	+	?	?	?
Sicilia 2005(40)	-	-	-	-
Sutherland 1992(41)	?	-	+	-
Timmer 1998(42)	-	-	+	-
Wright 1992(43)	-	-	-	-
<i>Outcome: Other adverse health outcomes among patients with IBD</i>				
Andrade 2018(29)	-	-	-	-
Lees 2009(37)	?	-	-	-
Lightner 2023(38)	-	-	+	-
<i>Outcome: Contraceptive effectiveness among IBD patients using oral contraceptives</i>				
Grimmer 1986(33)	-	+	?	-
Nilsson 1985(39)	-	+	?	-

Key:

-  + Low risk of bias
-  ? Moderate risk of bias
-  - High risk of bias

Figure 2. Risk of bias of evidence on the safety and effectiveness of contraceptive use among women with IBD

Table 1.

Evidence table for contraceptive use and IBD disease activity or relapse among patients with IBD

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results
Bitton 2001(30) United States and Canada R. Samuel McLaughlin Foundation, American College of Gastroenterology, Solvay Pharmaceuticals, and Procter and Gamble Pharmaceuticals	Prospective cohort study Patients enrolled over 20-months (years not reported) FU every 3 months until relapse occurred up to 1 year	42 women with UC in clinical remission ≥ 1 month and endoscopic remission at baseline Clinical setting (1 medical center and 1 hospital)	Intervention: Current OC use (definition not provided) Comparator: Never OC use OC use data available for 36/42 (86%) participants; distribution of OC use not reported	Time to UC relapse (defined as worsening of bowel function plus rectal bleeding with an endoscopic grade of 2, 3 or 4 with flexible sigmoidoscopy)	Current OC use was not associated with time to UC relapse compared with never OC use in crude (HR=2.1, 95% CIs not reported, $p>0.05$) or multivariable Cox regression analysis (data not shown; variables adjusted for not shown).
Cosnes 1999(31) France Source of support not stated	Prospective cohort study Recruitment occurred February 1995—January 1996 FU every 3–6 months for 12–18 months	331 women with CDAI <200 (aged 16–50 years) Clinical setting (1 outpatient unit)	Intervention: OC use, self-reported use during month before inclusion, 134/331 (40%) • 14 used POPs • 115 used 30–35 μg estrogen formulation • 5 used 50 μg estrogen formulation Comparator: Non-OC use, 197/331 (56%)	CD relapse (defined as increase of CDAI of at least 60 greater than baseline and exceeding 150; or development of abscess or new fistula in patients with chronic perianal disease) Time to CD relapse Median CDAI during relapse	CD relapse did not differ by OC use (p-value not significant): • 61/134 (46%) OC users • 85/197 (43%) non-users CD relapse did not differ by OC type: • 29% for POPs • 46% for 30–35 μg COCs • 40% for 50 μg COCs OC use was not associated with crude CD relapse compared with non-users (HR=1.11, 95% CI=0.80, 1.55). No evidence of effect modification by smoking status. When restricted to women with CDAI <150 (i.e., patients eligible for a relapse prevention trial), OC use was not associated with CD relapse (adjusted HR=1.26, 95% CI=0.71, 2.23 [adjusted for recent disease activity, anoperineal lesions, and smoking status]). No evidence of effect modification by smoking. Median time to relapse did not differ between OC users (484 days, SD=30 days) and non-OC users (504 days, SD=41 days). Median CDAI during relapse did not differ between OC users (246) and non-OC users (241).
Dolovich 2024 (32) Canada Canadian Institutes of Health Research	Prospective cohort study (nested within longitudinal Manitoba Living with IBD Study) Recruitment occurred June 2015—May 2017 FU biweekly via online surveys (HC assessed at baseline and weeks 14, 26, 40, and 52); stool samples	71 women with confirmed IBD (aged 18–49 years) who had IBD-related symptoms during the 2-year period before recruitment Recruited from multiple sources (previous cohort study, provincial population-based research registry, regional gastroenterology clinics, posters in clinical	Intervention: HC use*, self-reported use at baseline or any of the 4 FU time-points over 1 year FU period, 17/71 (24%) • 14 used COCs • 1 used POPs • 2 used LNG IUDs (1 Jaydess, 1 Mirena) Comparator: Non-HC use, 54/71 (76%) *COCs, POPs, LNG hormonal IUD (other methods of HC were not reported by participants)	Ever experienced during FU: IBD symptoms (defined as IBD SI >14 for CD, >13 for UC, or FCAL >250 mcg/g) Self-reported IBD flares Intestinal inflammation (defined as FCAL >250 mcg/g)	HC users had lower odds of IBD symptoms during the year compared with non-HC users (71% vs 94%; adjusted OR=0.16, 95% CI=0.02, 0.90). HC use was not associated with IBD flares during the year compared with non-HC use (59% vs 65%; adjusted HR=0.53, 95% CI=0.14, 1.93). HC users had higher odds of intestinal inflammation during the year compared with non-HC users (88% vs 63%; adjusted OR=5.7, 95% CI=1.23, 43.6). Multivariable models adjusted for age, disease type (UC or CD), disease duration, and smoking status.

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results																				
	provided at baseline and weeks 26 and 52)	offices, and online) (51)																							
Höie 2007(34) 7 European countries and Israel European Community (Grant QLG4-CT-200-01414)	Prospective cohort study (follow-up of a population-based inception cohort of IBD patients from 20 treatment centers) Recruitment occurred October 1991 — September 1993 FU for 10 years (interval not reported)	368 women with UC Clinical setting (9 treatment centers)	Intervention: OC use, use after UC diagnosis, 74/368 (20%) Comparator: Never OC use, 107/368 (29%) Other: Discontinued OC use before UC diagnosis, 66/368 (18%) No OC use data available, 121/368 (33%)	UC relapse (defined as increase in UC-related symptoms leading to changes in medical treatment or surgery) Time to first UC relapse Number of UC relapses during FU period	OC use was associated with the first UC relapse (HR=1.9, 95% CI=1.4, 2.7) during FU compared with never OC use in crude Cox regression analysis (including participants with no OC use data). Findings were no longer statistically significant in the multivariable model (data not shown; variables adjusted for not shown). OC use was associated with the total number of UC relapses during FU (HR=1.5, 95% CI=1.2, 1.8) compared with never OC use in crude Poisson regression analysis (including participants with no OC use data). Unclear if multivariable modeling was conducted. Time to first UC relapse: <table><tr><td></td><td>% (95% CI)</td></tr><tr><td><i>Before 2 years</i></td><td></td></tr><tr><td>OC users</td><td>55% (48-61%)</td></tr><tr><td>Never users:</td><td>36% (27-45%)</td></tr><tr><td><i>Before 5 years</i></td><td></td></tr><tr><td>OC users</td><td>77% (67-86%)</td></tr><tr><td>Never users:</td><td>51% (41-60%)</td></tr><tr><td><i>Before 10 years</i></td><td></td></tr><tr><td>OC users</td><td>86% (79-94%)</td></tr><tr><td>Never users:</td><td>59% (50-69%)</td></tr></table>		% (95% CI)	<i>Before 2 years</i>		OC users	55% (48-61%)	Never users:	36% (27-45%)	<i>Before 5 years</i>		OC users	77% (67-86%)	Never users:	51% (41-60%)	<i>Before 10 years</i>		OC users	86% (79-94%)	Never users:	59% (50-69%)
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Never users:	59% (50-69%)																								
Khalili 2016 <i>Gastro</i> (35) Sweden Crohn's and Colitis Foundation of America, American Gastroenterological Association, National Institute of Diabetes and Digestive and Kidney Diseases, American College of Gastroenterology	Prospective cohort study July 2005 (when OC use data became available) to December 31, 2013 Median FU was 58 months	4036 women with CD aged 16 —51 years Distribution of OC use presented for participants at midpoint of study in January 2008 (2521/4036, 62%) Nationwide registry	Intervention: Current OC use, updated monthly during FU from the Prescribed Drug Register, 641/2521 (25%) Comparator: Never OC use, 1338/2521 (53%) Other: Previous OC use, 542/2521 (22%) Additional exposures: Cumulative duration of OC intake Cumulative OC defined daily dose (DDD) – a measure of drug consumption defined by WHO to standardize the comparison of drug usage (used by study authors as a proxy of number of OC	First CD-related surgery First prescription for oral steroids after CD diagnosis	Compared with never OC use, current OC use was not significantly associated with risk of CD-related surgery (adjusted HR=1.30, 95% CI=0.89, 1.92). Incident rates per 100,000 person-months: • Never OC use: 18.2 • Current OC use: 22.6 The risk of CD-related surgery increased with longer duration of OC use (p-value for trend=0.036). Compared with never OC use, the adjusted HRs of CD-related surgery were: • 0.90 (95% CI=0.56, 1.45) with ≤1 year of OC use • 1.25 (95% CI=0.83, 1.90) with >1 and ≤3 years of OC use, and • 1.68 (95% CI=1.06, 2.67) with >3 years of use When examined by OC type (COCs and POPs), the risk of CD-related surgery increased																				

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results
			prescriptions) Progestin - containing IUD users compared with non-users		with longer duration of COC use ($p=0.041$) but not POP use ($p>0.50$). For COCs, with every 1 year of COC use, the risk of CD-related surgery increased by nearly 30% (adjusted HR=1.29, 95% CI=1.05, 1.57). The risk of CD-related surgery increased with higher number of DDDs of OC use (p-value for trend=0.016). Compared with never OC use, the adjusted HRs of CD-related surgery were: • 0.94 (95% CI=0.56, 1.58) with ≤ 300 DDDs of OC use • 1.25 (95% CI=0.82, 1.89) with >300 and ≤ 900 DDDs of OC use, and • 1.60 (95% CI=1.10, 2.34) with >900 DDDs of OC use When examined by OC type (COCs and POPs), the risk of CD-related surgery increased with higher number of DDDs of COC use ($p=0.02$) but not POP use ($p>0.50$). For COCs, with every 300 increase in DDD of COC use, the risk of CD-related surgery increased by 24% (adjusted HR=1.24, 95% CI=1.01, 1.52). Compared with never OC use, current OC use was not significantly associated with receiving an oral steroid prescription (adjusted HR=1.09, 95% CI=0.73, 1.64). Incident rates per 100,000 person-months: • Never OC use: 15.1 • Current OC use: 17.6 Also, the risk of receiving an oral steroid prescription did not increase with longer duration of OC use (p-value for trend=0.88) or with higher number of DDDs of OC use (p-value for trend=0.20). Results by OC type were not reported. Compared with non-use, progestin-containing IUD use was not significantly associated with risk of CD-related surgery (adjusted HR=0.98, 95% CI=0.69, 1.40) or receiving an oral steroid prescription (adjusted HR=1.03, 95% CI=0.71, 1.60). Multivariable models adjusted for age, number of encounters, duration of disease, and county.
Khalili 2016 <i>Am J Gastro</i> (36) Sweden Crohn's and Colitis Foundation of America, American Gastroenterological Association, National Institute of Diabetes	Prospective cohort study July 2005 (when OC use data became available) to December 31, 2014 Median FU	6104 women with UC aged 16—51 years Distribution of OC use presented for participants at midpoint of study in 2010 (3200/6104,	Intervention: Current OC use, updated monthly during FU from the Prescribed Drug Register, 572/3200 (18%) Comparator: Never OC use, 1812/3200 (57%) Other: Previous OC	First UC-related surgery First prescription for oral steroids at least 90 days after start of FU First prescription for anti-TNF	Compared with never OC use, current OC use was not significantly associated with risk of UC-related surgery (adjusted HR=0.74, 95% CI=0.46, 1.18). Incident rates per 100,000 person-years: • Never OC use: 527 • Current OC use: 495 The risk of UC-related surgery did

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results
and Digestive and Kidney Diseases, American College of Gastroenterology, Swedish Foundation for Strategic Research, Stockholm County Council, Bengt Ihre Research Fellowship in Gastroenterology, and the Mjölkdroppen Foundation	was 60 months	52%) Anti-TNF therapy analysis among patients from Stockholm county where data was available Nationwide registry	use, 816/3200 (26%) Additional exposures: Cumulative duration of OC intake Cumulative OC defined daily dose (DDD) – a measure of drug consumption defined by WHO to standardize the comparison of drug usage (used by study authors as a proxy of number of OC prescriptions)	therapy at least 90 days after start of FU	not appear to increase with longer duration of OC use (p-value for trend=0.28). Compared with never OC use, the adjusted HRs of UC-related surgery were: • 0.66 (95% CI=0.39, 1.13) with ≤ 1 year of OC use • 0.88 (95% CI=0.56, 1.39) with >1 and ≤ 3 years of OC use, and • 0.74 (95% CI=0.43, 1.27) with >3 years of use The risk of UC-related surgery did not appear to increase with higher number of DDDs of OC use (p-value for trend=0.70). Compared with never OC use, the adjusted HRs of UC-related surgery were: • 0.53 (95% CI=0.29, 0.99) with ≤ 300 DDDs of OC use • 0.83 (95% CI=0.52, 1.33) with >300 and ≤ 900 DDDs of OC use, and • 0.94 (95% CI=0.60, 1.47) with >900 DDDs of OC use Compared with never OC use, current OC use was not significantly associated with receiving an oral steroid prescription (adjusted HR=0.94, 95% CI=0.71, 1.26). Incident rates per 100,000 person-years: • Never OC use: 1,347 • Current OC use: 1,039 Also, the risk of receiving an oral steroid prescription did not increase with longer duration of OC use (p-value for trend=0.68) or with higher number of DDDs of OC use (p-value for trend=0.63). Associations between OC use and UC-related surgery and receiving an oral steroid prescription did not differ by OC type (COC or POP) among women who had used OCs for over two years. Compared with never OC use, current OC use was not significantly associated with receiving anti-TNF therapy (adjusted HR=0.83, 95% CI=0.59, 1.18). Incident rates per 100,000 person-years not reported. Also, the risk of receiving anti-TNF therapy did not increase with longer duration of OC use (p-value for trend=0.97) or with higher number of DDDs of OC use (p-value for trend=0.98). Multivariable models adjusted for age, age at diagnosis, number of encounters, education, and health care region of residence.
Sicilia 2005(40) Spain Source of support not reported	Prospective cohort study From CD diagnosis (1992—1995) to February 2001 Mean FU was	37 women with CD with at least 6 months of FU Data on OC use during FU available for 26/37 (70%) Clinical setting	Intervention: OC use during FU, 10/26 (38%) Comparator: Non-OC use during FU, 16/26 (62%)	CD relapse (defined as need for surgery)	No statistically significant differences in CD relapse comparing OC use with non-OC during FU in the bivariate analysis (data nor p-value were reported).

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results
	77 months (range 6-110); interval of FU not reported	(9 hospitals and multiple outpatient sites, healthcare sites, and private clinics from three provinces)			
Sutherland 1992(41) Canada Canadian Foundation of Ileitis and Colitis	Retrospective cohort study Years of data collection not reported Mean FU was 9.9 years (range 4-27)	97 women who underwent surgical resection for CD between 1966 and 1984 Aged 16–35 years at time of initial surgical resection Clinical setting (2 university-affiliated hospitals)	Intervention: OC use, self-reported use for ≥ 3 months during first year after initial surgery, 32/97 (33%) Comparator: Non-OC use, 65/97 (67%)	CD relapse (defined as need for repeat surgery to control CD episode)	No differences in CD relapse rates between OC users and non-OC users ($p>0.05$): • 11/32 (34%) OC users required additional surgery • 35/65 (53%) non-OC users required additional surgery. No differences in CD relapse rates between OC users and non-OC users ($p>0.05$) at 5 and 10 years: • 25% (95% CI=7, 43%) of OC users relapsed by 5 years, compared with 28% (95% CI=7, 43%) of non-OC users • 41% (95% CI=2, 80%) of OC users relapsed by 10 years, as compared with 64% (95% CI=41, 88%) of non-OC users. OC use was not associated with CD relapse compared with non-OC use in multivariable Cox proportional hazard modeling (data not shown; multivariable model appears to have adjusted for smoking, age, and disease location).
Timmer 1998(42) Canada Source of support not reported	Prospective cohort study (nested within a placebo-controlled trial of mesalamine in the maintenance therapy of CD) January 1990—January 1993 FU every 12 weeks until relapse occurred up to 48 weeks	75 placebo-assigned women with CD in remission (CDAI ≤ 150) aged 18–55 years Clinical setting (31 centers)	Intervention: Current OC use, self-reported use for ≥ 3 months at baseline, 28/75 (37%) Comparator: Never OC use, 30/75 (40%) Other: Previous OC use, 17/75 (23%)	CD relapse (defined as increase of CDAI of at least 60 greater than baseline and exceeding 150; or need for corticosteroids or hospitalization if CDAI not available)	Crude relapse rates significantly ($p<0.001$) differed: • 12/28 (43%) current OC users • 12/17 (70%) previous OC users • 8/30 (27%) never OC users Current OC use did not increase risk of relapse, compared with never OC use, after adjustment for smoking and type of remission (HR=1.7, 95% CI=0.7, 3.4).
Wright 1992(43) South Africa Harry Crosseley Fund	Prospective cohort study 1970—1988 FU from time of CD diagnosis to first relapse up to 10 years (mean=28.8 months)	162 women with CD diagnosed during study period Data on OC use at time of CD diagnosis available for 138/162 (85%) Clinical setting (1 hospital-based gastrointest inal clinic)	Intervention on: OC use at time of CD diagnosis, 51/138 (37%) Comparator: Non-OC use at time of CD diagnosis, 87/138 (63%)	Time to CD relapse Type of attack (no relapse, inflammatory, obstructive, other)	Mean time to first relapse was not associated with OC use at time of CD diagnosis. • 24.2 months (SD=26.7) for OC users. • 32.9 months (SD=38.0) for non-OC users. No statistically significant differences in type of attack by OC use at time of CD diagnosis.
					OC users n=51 Non-OC users n=87

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results		
					No relapse	22%	36%
					Inflammatory	57%	36%
					Obstructive	11%	19%
					Other	10%	9%

CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; COC, combined oral contraceptive pill; FCAL, fecal calprotectin; FU, follow-up; HC, hormonal contraception; HR, hazard ratio; IBD, inflammatory bowel disease; IBDSI, IBD Symptom Inventory; IUD, intrauterine device; LNG, levonorgestrel-releasing; OC, oral contraception; OR, odds ratio; POPs, progestin-only pills; NS, not significant; SD, standard deviation; TNF, tumor necrosis factor; UC, Ulcerative colitis; WHO, World Health Organization.

Table 2. Evidence table for contraceptive use and other adverse health outcomes among patients with IBD

Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results			
Andrade 2018(29) Brazil São Paulo Research Foundation	Retrospective cohort study Years of data collection not reported Mean FU not reported	627 women with IBD with image exams (ultrasound, CT, or MRI) performed January 2010 — May 2015 • 354 with CD • 273 with UC Clinical setting (1 tertiary hospital)	Intervention: OC use (definition not provided) Comparator: Non-OC use (assumed) Distribution of OC use not reported	VTE	In CD patients, OC use was not associated with VTE compared with non-OC use (OR=1.53, 95% CI=0.38, 6.2). 0 VTEs in OC users with UC			
Lees 2009(37) Scotland Source of support not reported	Retrospective cohort analysis 1977 —2007	362 women with IBD diagnosed before age 60 years with cervical smear records after IBD diagnosis (median age at diagnosis: 27.7 years; median current age: 44.7 years) • 184 with CD • 178 with UC Data on OC use available for 339/362 (94%) Clinical setting (1 tertiary referral center for IBD)	Intervention: Current OC use, 77/339 (23%) Comparator: Never-OC use, 47/339 (14%) Other: Previous OC use, 215/339 (63%)	Abnormal cervical smear results (rated as normal, low-grade dysplasia, or high-grade dysplasia) • For women who never had an abnormal smear, their most recent smear result was examined • For women who had an abnormal smear, their most abnormal smear result was examined	No statistically significant differences in abnormal cervical smear results in IBD patients by OC use.			
					OC Use	Normal	Low-grade dysplasia*	High-grade dysplasia**
					Current	66/77 (85.7%)	4/77(5.2%)	7/77(9.1%)
					Never	38/47 (80.9%)	8/47(17.0%)	1/47 (2.1%)
					Previous	184/215 (85.6%)	16/215 (7.4%)	15/215 (7.0%)
					p=0.106 *Low-grade: borderline or CIN I **High-grade: CIN II, CIN III, or higher			
Lightner 2023(38) United States Source of support not reported	Retrospective cohort study Years of data collection not reported FU for 90 days	16551 patients (men and women) with IBD aged >18 years with inpatient admission for IBD between January 1, 2002— January 1, 2020 (mean age 44.3±17.4 years at admission) • 11021 with CD • 5530 with UC 66,706 hospital admissions with complete data (unit of analysis for	Intervention: OC use (definition not provided) • 372/8664 (4%) among women • 372/16551 (2%) among men and women (multivariable models included both sexes) Comparator: Non-OC use	VTE (defined by imaging including ultrasound, CT, MRI, or interventional radiology describing a thrombus of the deep venous system or pulmonary venous system) • DVT during 90 days since hospital admission for IBD • PE during 90 days since hospital admission for IBD	OC use was not associated with DVT during 90 days since hospital admission for IBD compared with non-OC use (adjusted OR=0.57, 95% CI=0.21, 1.53; p=0.26). OC use was not associated with PE during 90 days since hospital admission for IBD compared with non-OC use (adjusted OR=2.56, 95% CI=0.75, 8.75; p=0.14). Multivariable models were adjusted for age, sex, BMI, tobacco use, disease type (UC vs CD), medical conditions, medication use, service type, and length of stay.			

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Author, year, location, funding source	Study design, years of data collection	Population	Intervention and comparison	Outcome	Results
		multivariable models) Clinical setting (1 quaternary IBD referral center)			

CD, Crohn’s disease; CI, confidence interval; CIN, cervical intraepithelial neoplasia; CT, computed tomography; DVT, deep venous thromboembolism; FU, Follow-up; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; UC, Ulcerative colitis; VTE, venous thromboembolism.

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Table 3.

Evidence table for contraceptive effectiveness among IBD patients using oral contraception

Author, year, location, funding source	Study design, years of data collection	Population	Exposure and comparison	Outcome	Results
Grimmer 1986(33) England Mersey Regional Health Authority, the World Health Organization, and the Medical Research Council	PK study/24 hours Participants received single dose of 50 mcg EE plus 250 mcg LNG after overnight fast • Once as oral dose • Once as IV infusion 10 mL blood samples drawn before Intervention dose and at 0.25 (infusion only), 0.5, 0.75 (infusion only), 1, 1.5, 2, 3, 4, 6, 8, 11, 14, and 24 hours after intervention dose Years of data collection not reported	10 women • 5 with UC who had undergone ileostomy at least 4 years prior involving only the colon (small bowel intact), aged 23—35 years, in good health, not on drug therapy • 5 healthy controls, aged 20—25 years Clinical setting	Exposure: Women with ileostomy following proctocolectomy Comparator: Healthy controls	Plasma concentrations of EE and LNG assessed by radioimmunoassay	Mean bioavailability of EE did not differ ($p>0.10$) • 55.4% (SD=10.9) for ileostomy group • 45.0% (SD=6.1) for control group Mean bioavailability of LNG did not differ ($p>0.10$) • 85.2% (SD=13.1) for ileostomy group • 104.6% (SD=22.3) for control group Peak concentration of EE did not differ ($p>0.10$) • 117 pg/mL (SD=21) for ileostomy group 1.5 hours after dosing • 169 pg/mL (SD=105) for control group 1.5 hours after dosing Peak concentration of LNG did not differ ($p>0.10$) • 4.72 ng/mL (SD=0.15) for ileostomy group 1.0 hour after dosing • 4.48 ng/mL (SD=0.8) for control group 2.0 hours after dosing
Nilsson 1985(39) Sweden Source of support not reported	PK study/10 hours Participants received single oral dose of 50 mcg EE plus 250 mcg LNG after overnight fast Blood samples drawn before Intervention dose and at 0.5, 1, 2, 4, 8 (controls), 10 (UC patients), and 12 (controls) hours after intervention dose Years of data collection not reported	20 women (mean age 29 ± 5 years) • 15 with UC (5 had unoperated mild-stage UC; 10, including 4 of previous 5, had proctocolectomy with continent ileostomy; 5, including 1 of previous 10, with conventional ileostomy) • 5 healthy controls Clinical setting	Exposure: Women with UC (non-operated; with conventional ileostomy following proctocolectomy; and with continent ileostomy following proctocolectomy) Comparator: Healthy controls	Plasma concentrations of LNG assessed by radioimmunoassay	Mean peak LNG levels did not differ among the unoperated patients or the conventional ileostomy patients when compared with controls (p-values not reported), but those with continent ileostomy had significantly lower LNG levels compared with controls ($p<0.05$). The 10-hour LNG values in UC patients with ileostomy did not statistically differ from controls (p-values not reported). However, ileostomy patients had significantly ($p<0.01$) lower LNG levels compared with patients with non-operated UC. Two patients with the largest resections (35 and 10 cm) from continent ileostomy had the lowest levels of LNG. No patient with ileostomy went below a 10-hour value of $1.7 \text{ nmol}\cdot\text{L}^{-1}$, a plasma level previously shown to be sufficient to inhibit ovulation.

COC, combined oral contraceptive pill; EE, ethinyl estradiol; IV, intravenous; LNG, levonorgestrel; OC, oral contraception; PK, pharmacokinetic; POPs, progestin-only pills; SD, standard deviation; UC, Ulcerative colitis.