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SYSTEMATIC REVIEW

Factors associated with decreased ovarian reserve in Crohn's disease: A systematic review and meta-analysis

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Abstract

Introduction: It is still unclear whether Crohn's disease (CD) might be associated with diminished ovarian reserve (OvR) and factors influencing anti-Mullerian hormone (AMH) levels in CD are poorly known.

Material and Methods: We conducted a comprehensive literature search of multiple electronic databases from inception to June 2022 to identify all studies reporting AMH levels or factors associated with diminished OvR in patients with CD.

Results: Of the 48 studies identified in our search, eight (including 418 patients with CD) were finally included. The mean difference (95% confidence interval [CI]) in the AMH level between pooled CD patients and controls was -0.56 (-1.14 to 0.03) ($p=0.06$). A history of CD-related surgery was not associated with a lower OvR (odds ratio, OR [95% CI] 1.34 , [0.66 – 2.7]; $p=0.4$). While disease activity and perianal disease seems associated with a low OvR, disease location (L2 vs. L1, OR [95% CI] = 95% CI [0.47 – 7.4]; $p=0.4$) and L3 vs. L1 (OR [95% CI] = 1.44 [0.67 – 3.12]; $p=0.3$), CD medication, and disease behavior were not.

Conclusions: Our systematic review and meta-analysis did not identify a significantly low OvR in patients with CD. Contrary to CD-related surgery risk factor, active disease was associated lower AMH levels.

KEYWORDS

anti-mullerian hormone, Crohn's disease, fertility, ovarian reserve, ulcerative colitis

1 | INTRODUCTION

Crohn's disease (CD) is a chronic, progressive, inflammatory disorder of the gastrointestinal tract that can alter quality of life and

lead to disability and irreversible bowel damage. Given that the median age at diagnosis is 29, CD is highly prevalent among women of childbearing age.¹ About half of patients with inflammatory bowel disease (IBD) are under 35 at the time of diagnosis, and one-quarter

Abbreviations: AMH, anti-Mullerian hormone; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; MD, mean difference; OR, odds ratio; OvR, ovarian reserve.

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become pregnant after the diagnosis.² IBD affects all aspects of a patient's life, including fertility.^{3,4} Although fertility (quantified as the number of children per woman or the percentage of pregnant women in the population) is normal in women with ulcerative colitis, a decrease in fertility of 17%–44% was observed in women with CD.⁵ In CD, many factors can influence fertility: voluntary childlessness, disease activity, malnutrition, a history of intestinal resection, etc. The weight of each of these factors remains to be determined, and a better understanding of the processes leading to the observed reduction in fertility in CD is required.

At the age of menarche, a woman has about 400 000 follicles.⁶ The decrease in the number of follicles accelerates in the mid-thirties.⁶ The term “ovarian reserve” (OvR) is employed to assess women's reproductive potential. The indicators used to gauge OvR aim to predict and evaluate the current pool of ovarian oocytes. It is important to note, however, that these markers do not necessarily correlate with the likelihood of spontaneous conception. The variables known to influence the OvR include age, genetic factors, and environmental factors.⁷ The decline in OvR is irreversible. However, predicting the decline in OvR is challenging in some diseases, such as cancer and immune-mediated inflammatory diseases. Biomarkers of OvR include the antral follicle count and the circulating levels of follicle-stimulating hormone or anti-Müllerian hormone (AMH).⁶ AMH is considered to be the most sensitive marker of OvR and is strongly correlated with primordial follicle pool.⁶

Several factors are associated with a fall in AMH levels; they include obesity, active smoking, chemotherapy, gynecological factors (endometriosis and ovarian surgery), and the presence of chronic inflammatory disease (such as systemic lupus erythematosus and rheumatoid arthritis).⁶ However, few studies have focused on AMH levels in IBD patient, and the available data are discordant due to the small sample sizes and interstudy difference in AMH assays. The results of two recent meta-analyses showed that OvR was significantly lower in patients with IBD, relative to the general female population.^{8,9} No specific data on OvR in women with CD are available, and the impacts of CD-related surgery, disease activity, behavior, or location have not been characterized.

We therefore conducted an up-to-date, rigorous, systematic review and meta-analysis of the literature data on AMH in women with CD and on factors associated with a decrease in OvR in this context. We sought to summarize current knowledge of the association between AMH levels and CD as a function of the patient profile, the disease history, and the phenotype.

2 | MATERIAL AND METHODS

This report complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards and followed a prespecified protocol.

Key message

Is Crohn's disease associated with diminished ovarian reserve? We did not evidence a significantly low ovarian reserve in patients with Crohn's disease. Contrary to Crohn's disease-related surgery, active disease was associated with lower anti-Müllerian hormone levels.

2.1 | Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE and ClinicalTrials electronic database (source: PubMed/ClinicalTrials; dates: 1966 to June 2022) with the following terms: “inflammatory bowel disease,” OR “Crohn's disease,” AND “ovarian reserve,” “AMH,” OR “anti-Müllerian hormone,” OR “ovarian function” OR “antral-follicle count,” OR “follicle-stimulating hormone.” The reference lists from review articles, meta-analyses, and observational studies were examined for additional publications. Two reviewers (A.F. and M.F.) independently assessed the titles and abstracts of studies identified in the initial PubMed search, according to pre-established inclusion criteria. The full text of the selected publications were then examined, in order to determine whether the inclusion criteria had been met: (i) a peer-reviewed observational cohort, cross-sectional or case-control study, (ii) English or French language, (iii) inclusion of patients with CD or IBD, and (iv) data on AMH levels or factors associated with diminished OvR in patients with CD. All the selected studies had been performed at referral centers or hospitals or were population-based studies. Inappropriate publications (such as letters, case reports, review articles, meta-analyses, and expert opinions) were excluded. Any disagreements between the two reviewers were resolved by consensus, after discussion with a third reviewer (N.R.).

2.2 | Data extraction

Data were extracted independently by two investigators (A.F. and N.R.), using a standardized data collection form. The following data were collected: (i) study characteristics: first author, study period, year of publication, country of the population studied, population source, number of included patients, and the length of follow-up; (ii) characteristics of the patients and the CD: age, disease duration, disease phenotype and site, history of intestinal resection, disease activity, perianal disease, and medications taken, and (iii) OvR: definition of the OvR used and AMH levels. Metrics of interest (such as the odds ratio [OR], relative risk, standardized mean difference [MD] or hazard ratio) and information on how they were calculated were collected whenever possible. Disagreements regarding data interpretation were resolved by consensus, after discussion with a third reviewer (M.F.).

2.3 | Statistical analyses

For the selected studies, the difference in the mean AMH level between patients with CD and those without CD and the corresponding 95% confidence interval (CI) were calculated in a meta-analysis. The ORs were calculated for discrete variables. The I^2 test was used to assess interstudy heterogeneity. Heterogeneity was taken into account with random-effects models, if required. A funnel plot was used to investigate publication bias. The threshold for statistical significance was set to $p < 0.05$. All analyses were performed using R software (version 4.1.3) and its “metafor,” “meta,” and “forestplot” packages.

3 | RESULTS

3.1 | Literature search

Of the 48 distinct publications identified in our search, eight (covering 418 patients with CD and an evaluation of OvR) were finally included (Figure S1; Table S1).^{10–17} All the studies had been conducted at referral centers. Five different countries were featured, and the patient enrollment periods ranged from 2010 to 2019. The study sample size ranged from 19 to 87 patients with CD. According to the Newcastle–Ottawa Scale, eight studies were considered to be of high quality (Table S1).

3.2 | CD and OvR

The MD (95% CI) in the AMH level between pooled CD patients and controls was -0.56 [-1.14 to 0.03] ($p = 0.06$) (Figure 1). The heterogeneity was significant ($I^2 = 81.0\%$; $p < 0.01$ in a Q-test). Seven studies, involving 330 CD patients, were included in this analysis^{10–13,15–17} (Study details in Table 1).

3.3 | Factors associated with low OvR in CD

3.3.1 | Surgery for CD

Three studies (covering a total of 187 patients) were analyzed.^{10,13,17} A history of CD-related surgery was not associated with a lower OvR

(OR [95% CI] 1.34, [0.66–2.7]; $p = 0.4$). There was no heterogeneity ($I^2 = 0$; $p = 0.51$ in a Q-test) (Figure 2). In two other studies (not included in the meta-analysis because of inhomogeneity of modality results), the difference in AMH levels between patients with or without a history of CD-related surgery was not significant for the 85 patients involved (Table 2).^{12,16}

3.3.2 | CD duration

Four studies (not included in the meta-analysis because of inhomogeneity of modality results) had evaluated the impact of the CD duration on OvR on 222 patients^{12,13,16,17} (Study details in Table 1). In Kadirogullari et al.'s study, AMH levels were significantly lower in patients with a CD duration > 5 years than in patients with a CD duration < 5 years (Table 2).¹² In Zhao et al.'s study, a disease duration of > 6 years was significantly associated with lower OvR (AMH ≤ 2 ng/mL) in a univariate analysis (OR [95% CI] = 2.64, [1.10–6.32]; $p = 0.03$) but not in a multivariate analysis.¹⁷ Two other studies did not find any influence of disease duration on the AMH level.^{13,16} In Koller et al.'s study, there was no difference in the median CD duration between a “low AMH” group and a “normal AMH” group (10 and 8 years, respectively; $p = 0.2$).¹³ In Şenates et al.'s study, there was no difference in the AMH level between patients with a CD duration > 5 years and patients with a CD duration < 5 years (Table 2).¹⁶

3.3.3 | Disease activity

Three studies (covering a total of 172 patients with CD) had evaluated the impact of CD activity on OvR (activity was defined as Crohn's Disease Activity Index > 150). All three found a significant negative impact of disease activity on OvR.^{12,16,17} Indeed, in Zhao et al.'s study, active disease was observed in 25 of the 30 patients (83.3%) in the “low AMH” (< 1.1 ng/mL) group and in 18 of the 57 patients (31.6%) in the “high AMH” group (OR [95% CI] = 36.3 [4.7–147.2], $p < 0.001$).¹⁷ In a multivariate analysis, Zhao et al. found that active disease was a risk factor for low AMH (< 1.1 ng/mL) (OR [95% CI] = 27.9 [6.1–127.9]; $p < 0.001$). In other studies, AMH levels were significantly lower in patients with active disease (Table 2).^{12,16,17}

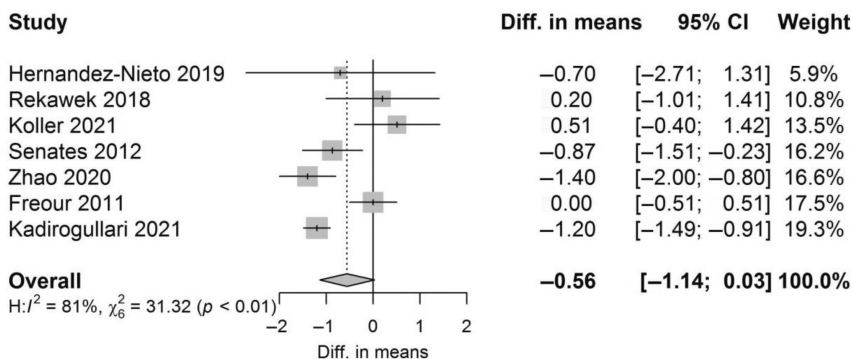


FIGURE 1 Mean difference [95% CI] in the anti-Mullerian hormone level between patients with Crohn's disease and controls. CI, confidence interval.

TABLE 1 Main characteristics of the reviewed studies.

Study	Study design	Source	Country	Time period	Participants (CD patients/controls)	CD factors evaluated	Main results
Fréour et al. ¹⁰	Single-center	Referral center	France; Nantes	UN	50/163	Surgery, behavior	No difference in the mean AMH level between patients with CD and controls
	Retrospective					Disease site, medication	Significantly more CD patients than controls with AMH <2 ng/mL
Kadiroglu et al. ¹²	Case-control						
	Single-center	Referral center	Turkish; Istanbul	03 to 08/2019	50/95	Surgery, duration	AMH levels were significantly lower in CD patients than in controls
	Prospective					Activity	AMH levels were significantly lower in patients with active CD
Koller et al. ¹³	Case-control						AMH levels were significantly lower when the CD duration was >5 years
	Multicenter	Referral center	Slovakia	2016	50/56	Surgery, behavior	No difference in the mean AMH level between patients with CD and controls
Peng et al. ¹⁴	Prospective		Bratislava			Disease site, medication	No risk factors for low AMH found
	Case-control					Duration	
Peng et al. ¹⁴	Single-center	Referral center	China	2016	88/78	Behavior	No risk factors for low AMH found
	Case-control		Guangzhou				
Şenates et al. ¹⁶	Single-center	Referral center	Turkish	2004–2010	35/35	Surgery, activity	AMH levels were significantly lower in patients with CD than in controls
	Case-control		Istanbul			Duration	AMH levels were significantly lower in patients with active CD
Zaho et al. ¹⁷	Single-center	Referral center	China	2013–2018	87/87	Disease site, medication	AMH levels were significantly lower in patients with CD than in controls
	Case-control		Guangzhou			Perianal disease	AMH levels were significantly lower in patients with active CD
Hernandez-Nieto et al. ¹¹	Single-center	Referral center	USA	2012–2018	19/114	Duration, behavior, activity	Disease activity was a significant risk factor for a low AMH level
	Retrospective		New York			AMH level	No difference in the mean AMH level between patients with CD and controls
Rekawek et al. ¹⁵	Case-control						
	Single-center	Referral center	USA	2010–2017	39/255	AMH level	No difference in the mean AMH level between patients with CD and controls
	Retrospective		New York				
	Case-control						

Abbreviations: AMH, anti-Müllerian hormone; CD, Crohn's disease.

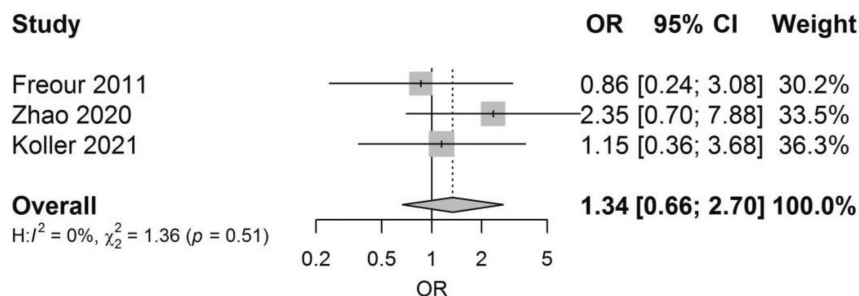


FIGURE 2 The OR [95% CI] for a low anti-Mullerian hormone level in patients with vs without Crohn's disease-related surgery. CI, confidence interval; OR, odds ratio.

3.3.4 | Disease behavior

Four studies (not included in the meta-analysis because of inhomogeneity of modality results) covering a total of 275 patients with CD investigated the effect of disease behavior on OvR.^{10,13,14,17} No significant associations were found (Table 3).^{10,13,14,17} CD behavior has three entities: (1) B1 non-stricturing, non-penetrating, (2) B2 stricturing and (3) B3 penetrating.

3.3.5 | Disease site

Three studies (covering a total of 187 patients with CD) had evaluated the impact of disease site on OvR.^{10,13,17} In a meta-analysis, there was no difference in OvR between patients with colonic disease (L2) and patients with ileal disease (L1) (OR [95% CI]=95% CI [0.47–7.4]; $p=0.4$). The level of heterogeneity was moderate ($I^2=48\%$; $p=0.15$ in a Q-test) (Figure 3A). Likewise, there was no difference in OvR between patients with ileocolonic disease (L3) and patients with ileal disease (L1) (OR [95% CI]=1.44 [0.67–3.12]; $p=0.3$). Again, there was no heterogeneity ($I^2=0\%$; $p=0.51$ in a Q-test) (Figure 3B).

3.3.6 | Perianal disease

A study of 87 patients with CD investigated AMH levels in individuals with perianal disease.¹⁷ The AMH level was significantly lower in patients with perianal CD than patients without perianal CD (Table 2). Perianal disease was observed in 15 of the 38 (65%) patients in the “low AMH” group and 8 of the 49 (19.5%) patients in the “normal AMH” group (OR [95% CI]=3.34 [1.23–9.07]; $p=0.02$). The AMH level was significantly lower in patients with perianal disease (1.57 ± 1.71 ng/mL, vs. 2.80 ± 2.12 ng/mL in patients without perianal disease; $p=0.015$).¹⁷

3.3.7 | Medication

Three studies (covering a total of 187 patients with CD) had evaluated the impact of IBD treatments on OvR.^{10,13,17} In Zhao et al.'s study, the AMH level was significantly lower in patients treated with thalidomide than in patients treated with other medications (steroids, azathioprine, or anti-tumor necrosis factor agents).¹³

Furthermore, Kadirogullari et al. did not find any difference in the AMH level between the 40 patients exposed to IBD medications (azathioprine: $n=12$; methotrexate: $n=8$; infliximab: $n=20$) and the 10 patients not exposed (2.6 ± 0.4 vs. 2.4 ± 0.8 , respectively; $p=0.9$).¹² The potential impact of each of the three medications was not reported¹² (Table 4).

4 | DISCUSSION

Through a systematic review and a meta-analysis covering eight studies and 418 patients, we sought to summarize current knowledge of the impact of CD-related factors on OvR. Our results showed that patients with CD did not have significantly a lower OvR than controls although the MD in the AMH level between pooled CD patients and controls was -0.56 ($p=0.06$). We found that disease activity was associated with a low OvR but that CD-related surgery, disease location, IBD medication, perianal disease, and disease behavior were not.

Anti-Mullerian hormone is produced by the granulosa cells of the preantral and antral follicles, and levels fall with age.¹⁸ The AMH level is related to the number of antral follicles¹⁸ and is a biomarker of OvR.¹⁹ Although the AMH level is a marker of the quantity of oocytes, it does not reflect the likelihood of a pregnancy.¹⁹ AMH is currently considered to be the most accurate hormonal marker of OvR. Studies have shown that a decrease in AMH levels of between 14% and 55% is observed in long-term (>1 year) users of hormonal contraception.¹⁹ Other factors have also been linked to abnormally low AMH levels, including a high body mass index, low vitamin D levels¹⁹ or chronic diseases such as rheumatoid arthritis or systemic lupus erythematosus. A significant reduction in fertility was observed in patients with CD,⁵ although the factors involved have yet to be identified. Recently, two meta-analysis reported a significant decrease in AMH levels in IBD patients; however, the disease-related factors responsible for this decrease remain to be determined—especially in a context of CD.

In patients with CD, disease activity appears to be the main driver of low fertility.^{20,21} Whereas fertility is not diminished in patients with inactive disease, a significant reduction in fertility occurs in the 9 months following a IBD flare.²⁰ Each of the three studies identified in our systematic review found a negative impact of disease activity on OvR. The international guidelines now

TABLE 2 Association between CD-related factors and the AMH level.

	AMH levels (ng/mL)	
	Mean \pm SD	p Value
CD-related surgery		
Kadirogullari et al. ¹²		
CD-related surgery (n=8)	2.3 \pm 0.7	0.2
No CD-related surgery (n=42)	2.5 \pm 0.8	
Şenates et al. ¹⁶		
CD-related surgery (n=6)	1.33 \pm 0.5	0.2
No CD-related surgery (n=29)	0.95 \pm 0.8	
Disease duration		
Kadirogullari et al. ¹²		
<5 years (n=23)	2.7 \pm 0.6	0.000
>5 years (n=27)	2.2 \pm 0.4	
Şenates et al. ¹⁶		
<5 years (n=23)	0.97 \pm 0.7	0.8
>5 years (n=27)	1.07 \pm 0.8	
Disease activity		
Kadirogullari et al. ¹²		
Active CD (n=21)	2.1 \pm 0.6	0.002
Remission (n=29)	2.6 \pm 0.8	
Şenates et al. ¹⁶		
Active CD (n=15)	0.33 \pm 0.25	<0.001
Remission (n=20)	1.53 \pm 0.5	
Zhao et al. ¹⁷		
Active CD (n=43)	1.34 \pm 1.4	<0.001
Remission (n=44)	3.52 \pm 2.1	
Perianal disease		
Zaho et al. ¹⁷		
Perianal disease (n=23)	1.6 \pm 1.7	0.015
Absence (n=64)	2.8 \pm 2.1	
Medication		
Zaho et al. ¹⁷		
Thalidomide (n=21)	0.89 \pm 0.93	<0.001
5-aminosalicylic acid (5-ASA)/no treatment (n=18)	3.08 \pm 1.85	
Thalidomide (n=21)	0.89 \pm 0.93	<0.001
Azathioprine (n=39)	2.89 \pm 2.08	
Thalidomide (n=21)	0.89 \pm 0.93	0.005
Steroids/infliximab (n=9)	3.12 \pm 2.79	

Abbreviations: AMH, anti-Mullerian hormone; CD, Crohn's disease.

state that active disease is associated with decreased fertility in women with IBD and that achieving clinical remission may increase the probability of successful conception.²² It has been suggested that systemic inflammation does not favor conception, and so a decrease in OvR might be an explanation. The CD-related inflammatory burden related has an important role in diminished fertility,

TABLE 3 Association between CD behavior and the AMH level.

	Patients with a low AMH level/n (%)	Patients with a normal AMH level/n (%)	Univariate analysis	
			OR [95% CI]	p
Fréour et al. ¹⁰				
B1	21 (87.5)	14 (53.8)	-	0.9
B2	2 (8.3)	8 (30.8)	-	0.5
B3	1 (4.2)	23 (88.4)	-	1
Zhao et al. ¹⁷				
B1	23 (60.5)	39 (79.6)		
B2	11 (28.9)	5 (10.2)	3.70 [1.15–12.09]	0.028
B3	4 (10.5)	5 (10.2)	1.36 [0.33–5.57]	0.672
Koller et al. ¹³				
B1	10 (52.6)	17 (54.8)	-	1
B2	4 (21.1)	10 (32.3)	-	0.522
B3	5 (26.3)	4 (12.9)	-	0.273
Peng et al. ¹⁴				
B1	15 (48.4)	37 (64.9)		
B2	9 (29)	13 (22.8)	1.8 [0.63–5.1]	0.3
B3	7 (22.6)	7 (12.3)	2.4 [0.71–8.03]	0.2

Abbreviations: AMH, anti-Mullerian hormone; CD, Crohn's disease; CI, confidence interval; OR, odds ratio.

even when the gynecological system is structurally normal. Some experts have speculated that antibody disorders and a disrupted immune response are responsible for the diminished OvR observed in patients with IBD.⁸ Malnutrition, folate deficiency, or vitamin D deficiency associated with period of remission might also have a role.^{23–25} The long-term course and potential reversibility of these changes remain to be characterized.

It is not clear whether CD-related surgery affects fertility.²⁶ Several studies have reported that CD-related surgery is associated with an increased risk of infertility.²⁷ With the exception of open pouch techniques, it appears that CD-related intestinal resection is not associated with an increased risk of infertility; however, the data are contradictory.^{22,28} Our meta-analysis did not evidence an association between CD-related surgery and OvR.²²

It has been hypothesized that the CD site has an influence on fertility and OvR. In our meta-analysis, neither the disease site nor disease behavior was associated with a decrease in OvR. Furthermore, some drugs used in the treatment of CD might have effects on OvR. This is clearly the case for thalidomide, although this drug is no longer prescribed for CD in clinical practice. The biologics and small molecules used to treat IBD are not thought to be associated with a low OvR, although few data have been published.²²

This study had several limitations. As with all systematic reviews and meta-analyses of observational and retrospective studies, interpretation of the results is limited by the number, quality and homogeneity of the included studies. If few studies are included,

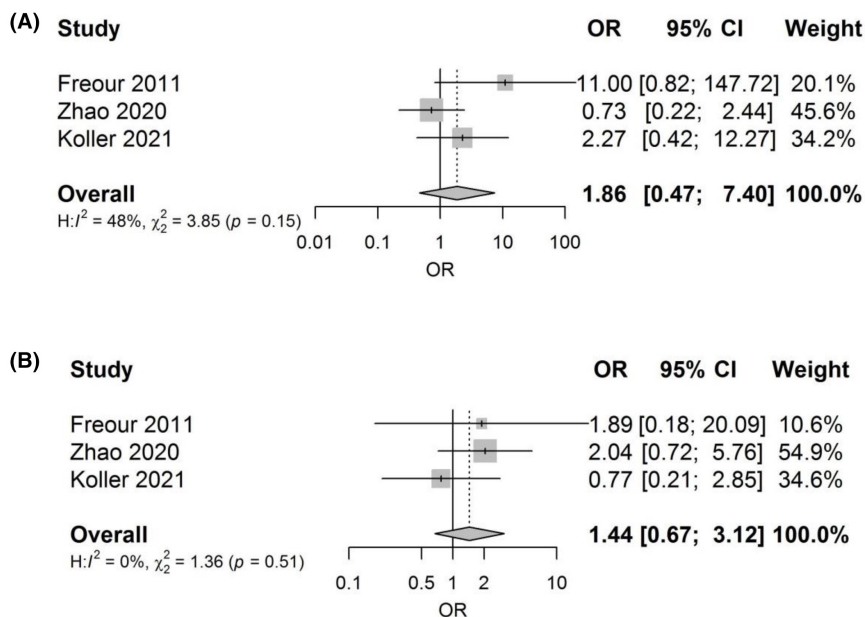


FIGURE 3 The OR [95% CI] for a low anti-Mullerian hormone level in patients (A) with colonic disease (L2) vs ileal disease (L1) and (B) ileocolonic disease (L3) vs ileal disease (L1). CI, confidence interval; OR, odds ratio.

TABLE 4 Association between CD medications and the AMH level.

	Patients with a low AMH level	Patients with a normal AMH level	Univariate analysis		Multivariate analysis			
			n (%)	n (%)	OR [95% CI]	p	OR [95% CI]	p
Fréour et al. ¹⁰	N=24	N=25						
Azathioprine	14 (58.3)	14 (53.8)	-	0.9	-	-	-	-
Methotrexate	5 (20.8)	8 (30.8)	-	0.5	-	-	-	-
Infliximab	21 (87.5)	23 (88.4)	-	1	-	-	-	-
Zhao et al. ¹⁷	N=38	N=49						
5-ASA/No treatment	6 (15.7)	12 (24.5)	Ref	-	-	-	-	-
Steroids/infliximab	3 (7.9)	6 (12.2)	1 [0.18–5.46]	0.999	-	-	-	-
Azathioprine	12 (31.6)	27 (55.1)	0.89 [0.27–2.93]	0.85	-	-	-	-
Thalidomide	17 (44.7)	4 (8.2)	8.5 [1.96–36.79]	0.004	15.66 [2.22–110.65]	0.006	-	-
Koller et al. ¹³	N=19	N=31						
Steroids	0	2 (6.5)	-	0.5	-	-	-	-
Amnisalicylates	2 (10.5)	18 (58.1)	-	0.8	-	-	-	-
Azathioprine	10 (52.6)	19 (61.3)	-	0.6	-	-	-	-
Anti-TNF agents	12 (63.2)	18 (58.1)	-	0.8	-	-	-	-

Abbreviations: AMH, anti-Mullerian hormone; CD, Crohn's disease; CI, confidence interval; OR, odds ratio; TNF, tumor necrosis factor.

meta-regression cannot be used reliably to identify prespecified sources of heterogeneity that might be linked to factors like the study period, the geographic locations, and the AMH assay protocols. Although a few studies controlled for important variables (such as age and body mass index), adjusted ORs or standardized MDs were rarely reported. We performed a meta-analysis when at least three studies contained the necessary data; this was not the case for all the factors of interest. These limitations emphasize the need for more research on factors influencing the OvR in CD.

5 | CONCLUSION

Our systematic review and meta-analysis did not identify a significantly low OvR in patients with CD. We found that disease activity was associated with a low OvR but that CD-related surgery, disease location and behavior were not. The association with disease activity might be due to both the direct influence of the inflammatory response and to indirect influences of CD therapeutics, nutrient deficiencies, psychological disorders, and decreased quality of life. While

waiting for more data, we hope that our results will be of use in the multidisciplinary management of CD in women of childbearing age.

AUTHOR CONTRIBUTIONS

Arthur Foulon and Mathurin Fumery were involved in data collection and analyses, writing and revising the manuscript. Nicolas Richard and Camille Guichard were involved in data collection and revising the manuscript. Clara Yzet, Coraline Breuval, Jean Gondry, and Rosalie Cabry-Goubet were involved in the revising the manuscript. Audrey Michaud was involved in the statistical analysis and revising the manuscript.

CONFLICT OF INTEREST STATEMENT

Mathurin Fumery: Consulting/lecture fees for Abbvie, Amgen, Arena, Biogen, Celtrion, CTMA, Galapagos, Janssen, MSD, Pfizer, Takeda, Fresenius-Kabi, Tillotts, MSD, Gilead, Celgene, Sandoz, and Ferring. Clara Yzet: Consulting/lecture fees for Abbvie, Janssen, Takeda, Galapagos, and Amgen. The remaining authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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