

# Ovarian reserve and IVF outcomes in patients with inflammatory bowel disease: A systematic review and meta-analysis

Honghao Sun,<sup>a,e</sup> Jiao Jiao,<sup>a,e</sup> Feng Tian,<sup>b</sup> Qing Liu,<sup>c</sup> Jiansu Bian,<sup>a,e</sup> Rongmin Xu,<sup>b</sup> Da Li,<sup>a,e,\*</sup> Xiuxia Wang,<sup>a,e,\*</sup> and Hong Shu<sup>d,\*</sup>

<sup>a</sup>Center of Reproductive Medicine, Shengjing Hospital of China Medical University, Shenyang, China

<sup>b</sup>Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang, China

<sup>c</sup>Key Laboratory of Health Ministry for Congenital Malformation, Shengjing Hospital of China Medical University, Shenyang, China

<sup>d</sup>Department of Pathology, Shengjing Hospital of China Medical University, Shenyang, China

<sup>e</sup>Shenyang Reproductive Health Clinical Medicine Research Center, Shenyang, China

## Summary

**Background** Inflammatory bowel disease (IBD) mainly affects people during reproductive age. However, it is unclear whether IBD might be associated with impaired ovarian reserve in female patients or with in vitro fertilization (IVF) outcomes.

**Methods** This systematic review and meta-analysis included articles from inception to May, 2022. Random-effect model was applied to calculate the standardized mean differences (SMDs) and odds ratios (ORs) and their 95% confidence intervals (95% CIs). Studies comparing the ovarian reserve or IVF outcomes of patients with IBD with the population were considered. To be included in this study, necessary measurements such as OR, relative risk (RR), SMD or hazard ratio (HR) or any necessary information to calculate them were provided in the articles. Letters, case reports, review articles including meta-analyses and expert opinions were excluded. For different articles studying the same population, the article with larger scale was selected.

**Findings** We included in our analysis 9 studies and data from 2386 IBD records and matched controls. Comparing with women without IBD, women with IBD had lower anti-mullerian hormone (AMH) levels (SMD = -0.38, 95%CI: -0.67, -0.09); ( $I^2 = 79.0\%$ ,  $p = 0.000$ ). Patients with IBD of different ages showed distinct ovarian reserves, with patients below 30 years old not showing any decline in ovarian reserve compared to the control group (SMD = -0.56, 95%CI: -2.28, 1.16); ( $I^2 = 96.3\%$ ;  $p = 0.000$ ), while patients with IBD over 30 years old (SMD = -0.75, 95%CI: -1.07, -0.43); ( $I^2 = 0.0\%$ ;  $p = 0.608$ ) showed a decline compared to control group. Patients with IBD in remission stage had similar ovarian reserves to population (SMD = -0.10, 95%CI: -0.32, 0.12); ( $I^2 = 0.0\%$ ;  $p = 0.667$ ), while patients in active stage showed an impaired ovarian reserve (SMD = -1.30, 95%CI: -1.64, -0.96); ( $I^2 = 0.0\%$ ;  $p = 0.318$ ). Patients with IBD showed a pregnancy rate after receiving IVF treatment comparable to the control population (OR = 0.87, 95%CI: 0.55, 1.37); ( $I^2 = 70.1\%$ ,  $p = 0.035$ ).

**Interpretation** The result of this study suggest that IBD may reduce reproductive age women's ovarian reserve and IVF treatment might help pregnancy outcomes in patients with impaired fertility. These results should be further validated in additional studies given the heterogeneity and quality of the studies included.

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**Keywords:** PCOS; IVF; AMH; Pregnancy outcomes

\*Corresponding authors at: Center of Reproductive Medicine and Department of Pathology, Shengjing Hospital, China Medical University, No. 36, SanHao Street, Shenyang 110004, China.

E-mail addresses: [Leeda@ymail.com](mailto:Leeda@ymail.com) (D. Li), [Wangxjsj@126.com](mailto:Wangxjsj@126.com) (X. Wang), [Shuhong302@hotmail.com](mailto:Shuhong302@hotmail.com) (H. Shu).

### Research in context

#### *Evidence before this study*

PubMed, Embase and Web of Science were searched for all studies published from inception to May 2022 concerning the ovarian reserve of inflammatory bowel disease (IBD) patients and their in vitro fertilisation (IVF) outcomes. The following terms were used: “ovarian reserve”, “AMH”, “anti mullerian hormone”, “antral follicle count”, and “assisted reproductive technology”, “embryo transfer”, “in vitro fertilization”, and “inflammatory bowel disease”, “Crohn’s disease”, “ulcerative colitis”. No language limitation was applied. To the best of our knowledge, this is the first study assessing the ovarian reserve and IVF outcomes of patients with IBD.

#### *Added value of this study*

The result of this study suggests that IBD may reduce reproductive age women’s ovarian reserve. IBD patients in remission stage have comparable ovarian reserves to healthy individuals, and patients with women receiving IVF treatment could have comparable pregnancy outcomes compared with control group.

#### *Implications of all the available evidence*

A systematic assessment should be carried out to balance fertility and disease control for female patients with IBD who plan to conceive a child in the near future.

## Introduction

Inflammatory bowel disease is a chronic disease of alimentary canal characterized by diarrhea, abdominal pain, and tenesmus. It can be further divided into ulcerative colitis (UC) and Crohn’s disease (CD). The incidence of IBD varies with geographical location, high incidence areas including Europe, North America and Oceania, where over 0.3% of the population suffer from IBD.<sup>1</sup> However, the difference between high-income countries and newly industrialized countries is narrowing.<sup>2</sup> The disease fluctuates with time periodically. Remission stage refers to when the bowel form is normal and abdominal symptoms are minor, whereas the active stage is characterized by altered bowel form, ulcerated mucosa and severe clinical symptoms. In IBD, abdominal symptoms such as diarrhea, nausea, abdominal pain and systemic symptoms (fever, malnutrition and weight loss) exist simultaneously. IBD mainly affects young people in their reproductive ages. The median age at diagnosis was 29.5 and 34.9 for CD and UC respectively.<sup>3</sup> Various pieces of researches have reported a decreased fertility in IBD females,<sup>4</sup> and it is still unknown whether fertility decrease can be attributed to impaired ovarian reserve.

Anti-mullerian hormone (AMH) is a member of the transforming growth factor $\beta$  (TGF- $\beta$ ) superfamily,<sup>5</sup> secreted by granulosa cells of the preantral and antral follicles. Its concentration is not affected by menstrual cycle and pregnancy. Therefore, the level of AMH is the best parameter for the prediction of ovarian reserve and fertility. Recently, several researches have been carried out on the impact of IBD on the AMH levels of reproductive-age females. But due to the diversity in race, measuring methods and age, their results were inconsistent. Furthermore, women with IBD suffer from declined fertility and a higher sexual dysfunction rate than the healthy population.<sup>6</sup> IVF is one of the most broadly used solutions for infertility and has a wide range of applications, often used in the treatment of tubal infertility, anovulatory infertility and male factor infertility. It is still unclear whether IVF can improve IBD patients’ fertility to match their healthy counterparts.

Females with IBD also have childbearing demands. However, IBD comprises systemic symptoms, and other influences such as malnutrition, mental health issues, and IBD patients may receive abdominal surgeries. All these factors will negatively affect female fertility. Thus, a systematic evaluation and comprehensive therapy should be applied to improve fertility and balance fertility and the control of disease. This study aims to explore the association between decreased fertility and impaired ovarian reserve in IBD females and to assess whether IBD females received IVF can be treated to comparable pregnancy outcomes with healthy people.

## Methods

### Search strategy and selection criteria

This systematic review and meta-analysis were performed and all data was extracted under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In this study, a comprehensive search was performed on PubMed, Embase and Web of Science from inception to May, 2022. All potential studies concerning ovarian reserve of IBD patients and their IVF outcomes were viewed. Only human studies were considered and no language restriction was applied. A combined search strategy was used. For ovarian reserve, the following terms were used: “ovarian reserve”, “AMH”, “anti mullerian hormone”, “antral follicle count”, for IVF outcome, the following terms were used: “assisted reproductive technology”, “embryo transfer”, “in vitro fertilization”, for IBD, the following terms were used: “inflammatory bowel disease”, “Crohn’s disease”, “ulcerative colitis”. Two investigators (W.X.X. and S.H.H.) separately reviewed the titles and abstracts of the articles. Potentially eligible studies were selected for full-text screening. Irrelevant studies were excluded after full-text reading according to pre-

specified inclusion and exclusion criteria. We also performed a recursive search on the reference lists of relevant studies to identify additional eligible studies. Ethics approval was not required for meta-analyses due to no human subjects were involved and studies previously published and based on anonymized data were used.

Two investigators (W.X.X. and S.H.H.) conducted the literature search independently. Only observational studies, for instance, cohort studies, cross-sectional studies and case-control studies comparing the ovarian reserve or IVF outcomes of IBD patients with normal control population were included in this study. Participants were restricted to adults, articles studying adolescents were excluded. The necessary measurements such as OR, relative risk (RR), standardized mean difference (SMD) or hazard ratio (HR) should be provided in the articles, otherwise, other necessary information to calculate them should be available. Inappropriate researches, such as letters, case reports, review articles including meta-analyses and expert opinions were removed. Studies should have ethical approval to share data and contain 30 or more participants, studies lack adequate information or do not have appropriate control group were also excluded. For different articles studying the same population, only the study with largest scale was included. Studies published in abstract form were eligible for inclusion if they could provide adequate information. Dispute on eligibility would be solved by discussion among two investigators (W.X.X. and S.H.H.). Kappa statistic was used to evaluate inter-examiner agreement on study eligibility. When disagreement appeared between the investigators, two other reviewers (S.H. and L.D.) will resolve the disagreement. All authors take part in study selection, data extraction and quality assessment were clinicians from Shengjing hospital affiliated to China Medical University. And have all took part in similar studies before. Two reviewers would make decision first and other two would check it and solve disagreements

#### Data analysis

Necessary information was extracted by two independent reviewers (W.X.X. and S.H.H.) after full text reading, including title, name of author, publication year, geographic region, study design, diagnostic criteria for IBD, characteristics of IBD patients and control group and the number of PCOS population and control population. For articles comparing ovarian reserve of IBD patients with normal population, the AMH value and its detection method and the IBD disease stage during detection were also extracted. For articles comparing IVF outcomes of IBD patients with normal population, the following messages were also extracted: pregnancy rate, live birth rate, causes of infertility, the protocol of controlled ovarian hyperstimulation, method of

fertilization. Data extracted was written into a Microsoft Excel spreadsheet by two reviewers respectively and check with each other.

Two investigators (W.X.X. and S.H.H.) assessed the quality of the included articles using the Newcastle-Ottawa Scale (NOS) separately. If any disagreement arose, two other reviewers (L.D. and S.H.) would solve the dispute. The degree of consistence of the NOS score between the two investigators were measured by kappa statistic, kappa statistics between 0.61 and 0.80 were regarded as substantial agreement and kappa statistics >0.80 were regarded as almost perfect agreement. Only high quality (obtaining  $\geq 70\%$  of the highest score) and moderate quality (obtaining 40-70% of the highest score) articles would be included.

The ovarian reserve and IVF outcomes of IBD patients compared with matched control group were evaluated by the standardized mean differences (SMDs) or odds ratios (ORs) and 95% confidence intervals (CIs). Significantly heterogeneity was found and the random-effects model was applied. Heterogeneity was assessed by  $I^2$  statistic and the Cochran's Q test. Subgroup analyses on the type of IBD, geographic region and study design were conducted to explore the source of heterogeneity. Begg's test and Egger's test were applied to detect potential publication bias. The statistical analysis was performed using Stata software 11.0. To further evaluate the different influence of different stage of IBD on ovarian reserve and its impact on women of different ages, we also performed subgroup analyses on disease stage and age.

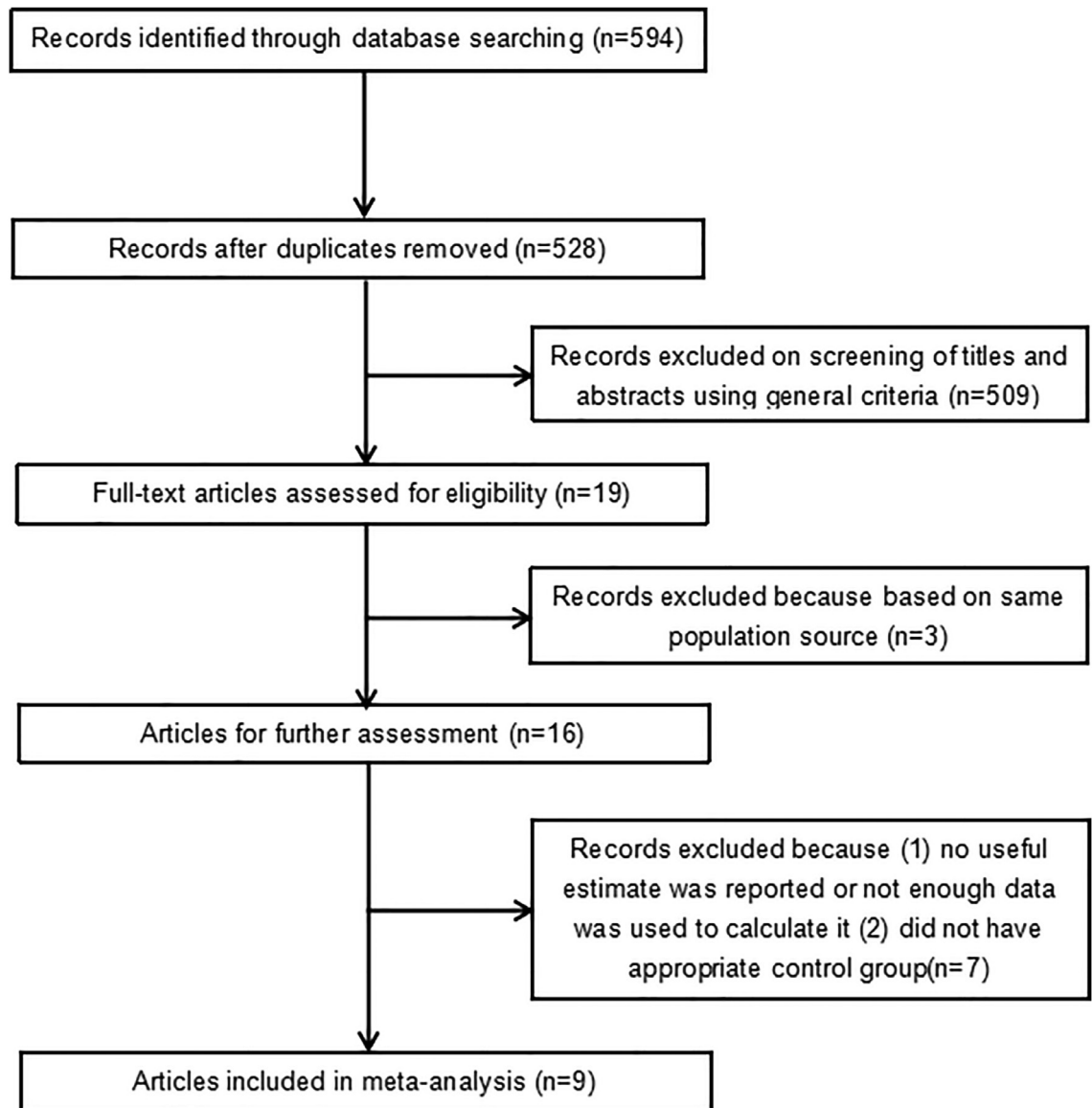
#### Role of the Funding Source

The funders had no role in the design, data collection and interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

#### Literature search

The literature search identified 594 citations using our search strategy as [Figure 1](#) showed. 66 studies were removed due to duplication. Two investigators reviewed the titles and abstracts of the rest articles, 509 articles with irrelevant titles and abstracts were excluded using the given inclusion and exclusion criteria. The full-text of rest 19 relevant citations were reviewed. Three studies were then excluded because they are based on same population source.<sup>7-9</sup> Seven articles were excluded because the risk ratio was not provided or they did not have an appropriate control group.<sup>10-16</sup> Nine articles finally meet the eligibility criteria for inclusion.<sup>17-25</sup> There was almost perfect agreement between the two reviewers in judging eligibility of the citations (kappa



**Figure 1.** Flow diagram of the assessment of studies identified in the systematic review.

statistic = 0.854). Two articles were moderate quality<sup>17,21</sup> judged by NOS score system while the rest studies were high quality.<sup>18–20,22–25</sup>

**Study characteristics**

In Table 1 we summarized the characteristics of the included articles. We finally included 9 studies involving 2386 IBD records and 149742 records of matched controls, in some articles evaluating IVF outcomes, some patients received more than one cycle of IVF treatments. Among those 9 studies, 5 were retrospective cohort studies and 4 were case-control studies. Three studies were performed in European countries, three in

Asian countries and three in America. Their publication date varied from 2012 to 2020. Six studies assessed the ovarian reserve of IBD patients and four studies assessed the IVF outcomes of the IBD patients. Among those studies, one article assessed both the ovarian reserve and IVF outcomes of IBD patients,<sup>24</sup> so it was included in both the calculation of ovarian reserve and IVF outcomes. Two articles were conducted by different authors but concerning a same population. One of them assessed both the pregnancy rate and live birth rate of IBD patients at the same time,<sup>21</sup> another article only assessed live birth rate of IBD patients,<sup>20</sup> but it included more participants and are more detailed. So, we use the data from the first article in the calculation

Country	Study design	Year	Number of IBD	Number of control	Characteristics of IBD	Characteristics of control	Diagnostic criteria of IBD	IBD stage	Criteria for control	NOS score	AMH of IBD	AMH of control	Detection method of AMH				
Freour T	France	Retrospective case-control study	IBD: 50; CD: 50	163	Age: 30.0±6.2	Age: 31.9±3.6	Judged by clinical, radiological, endoscopic, and histological features	All clinical remission	Reproductive age, both ovaries present, no previous exposure to cytotoxic drugs or pelvic radiation therapy, no known systemic, endocrine, or metabolic disease, and normal ovarian status, no PCOS	6	3.12±1.7	3.12±1.2	Blood sample, Immunotech, Beckman Coulter method				
Zhao Y	China	Case-control study	IBD: 87; CD: 87	87	Age: 30 (18-45); BMI: 20.4±2.3	Age: 30 (18-45); BMI: 21.4±2.8	Age: 18-45, judged by clinical manifestations and endoscopic, radiologic, and histopathological findings	43 active stage and 44 remission stage	Recruited from local communities. Controls were matched for age, height and weight in a 1:1 ratio, non-pregnancy and not taking oral contraceptive.	9	2.47±2.08	3.87±1.96	Blood sample, Elisa				
Peng X	China	Case-control study	IBD: 106; CD: 88; UC: 18	78	Age: 26.54±6.61	Not mentioned	Judged by symptoms, physical condition, endoscopy, radiology, and pathology	45 active disease state and 61 remission	Not mentioned	8	2.11±1.96	5.61±5.06	Whole blood sample, Elisa				
Senates E	Turkey	Case-control study	IBD: 35; CD: 35	35	Age: 34±5; BMI: 26.6±5.3	Age: 33±5; BMI: 24.5±4.2	Judged by endoscopic, radiologic and histopathologic findings	15 active stage and 20 remission stage	Healthy, age-matched women	7	1.02±0.72	1.89±1.80	Blood sample, Elisa				
P. Rekawek	America	Retrospective cohort study	IBD: 85; CD: 39; UC: 46	255	Age: 34.9±4.6	Age: 34.7±4.6	Medical records	Not mentioned	3 controls (matched by age and year of the electronic medical record database)	8	IBD: 2.94±3.99; UC: 2.73±4.32; CD: 3.19±3.6	2.99±3.46	Not mentioned				
Hernandez-Nieto	America	Retrospective cohort study	IBD: 38; CD: 19; UC: 19	114	Age: 34.5±4.3; BMI: 22.8±3.1	Age: 34.6±3.8; BMI: 23.5±3.9	Medical records, ICD-9 code	Not mentioned	Matched 3:1 cohort of control subjects were identified using a propensity-score matching algorithm based on clinical parameters	8	IBD: 3.23±2.8; UC: 2.94±2.17; CD: 3.78±3.93	4.5±5.4	Not mentioned				
Friedman S	Denmark	Cohort study	IBD: 1900; CD: 552; UC: 1348	147348	Not mentioned	Not mentioned	Medical records, ICD-8&10 codes	Not mentioned	Women without IBD from the same dataset	6	IBD: 408; CD: 107; UC: 301	40552	IBD: 337; CD: 89; UC: 248 (not included in analysis)	32241	Not mentioned	IVF or ICSI	Fresh or frozen
Pabby V	America	Retrospective cohort study	IBD: 71; CD: 71	470	Median (interquartile range) Age: 35.6 (33.0-39.5) for no IPAA patients; 33.9 (32.1-37.3) for IPAA patients	Median (interquartile range) Age: 35.2 (32.6-39.2); BMI: 24.0 (21.5-28.0)	Medical records, ICD-9 codes	Not mentioned	Match four women without IBD to each woman with IBD on the basis of age	8	IBD: 35; UC: 35	192	IBD: 24; UC: 24	142	Standard IVF protocols based on the patient's age, infertility diagnosis, and ovarian reserve assessment	IVF or ICSI	Not mentioned
Hernandez-Nieto	America	Retrospective cohort study	IBD: 38; CD: 19; UC: 19	114	Age: 34.5±4.3; BMI: 22.8±3.1	Age: 34.6±3.8; BMI: 23.5±3.9	Medical records, ICD-9 codes	Not mentioned	A matched 3:1 cohort of control subjects were identified using a propensity-score matching algorithm based on clinical parameters	8	IBD: 19; CD: 7; UC: 12	69	IBD: 17; CD: 6; UC: 11	65	Conventional controlled ovarian stimulation	ICSI	Frozen blastocysts
Norgard BM	Denmark	Cohort study	IBD: 1914; CD: 554; UC: 1360	148540	Age: Median (25-75 centiles) UC: 33 (30-36); CD: 32 (30-35)	Age: Median (25-75 centiles) UC: 33 (30-37)	Medical records, ICD-8&10 codes	Not mentioned	Women without IBD from the same dataset	7	Not mentioned	Not mentioned	IBD: 366; CD: 94; UC: 272	35321	Not mentioned	IVF or ICSI	Fresh or frozen

Table 1: Characteristics of the included studies.

IBD=Inflammatory bowel disease. NOS=Newcastle-Ottawa Scale. AMH=anti-müllerian hormone. CD=Crohn's disease. UC=ulcerative colitis. PCOS=polycystic ovary syndrome. BMI=body mass index. ICD=International Classification of Disease. IVF=in vitro fertilization. ICSI=intracytoplasmic sperm injection. IPAA=ileal pouch-anal anastomosis.

of pregnancy and data from the second article in the calculation of live birth rate. Among these studies, three articles<sup>17,18,25</sup> concerned only CD patients and 1 article<sup>19</sup> studied only UC patients, the rest 5 articles studied both type of IBD patients. Three articles performed subgroup analyses of IBD patients' AMH grouped by age. Another 3 articles performed subgroup analyses of IBD patients' AMH disease stage.<sup>17,18,25</sup> Four studies made the diagnosis of IBD based on clinical, radiological, endoscopic, and histological features,<sup>17,18,22,25</sup> three studies made the diagnosis based on medical records<sup>19,23,24</sup> and another 2 studies made the diagnosis based on register data.<sup>20,21</sup> Most of the articles selected the control group from the same population and matched with clinical factors such as age and disease duration. There was no substantial publication bias found in funnel plot and in Begg's test and Egger's test. Substantial agreement was achieved between the two reviewers when accessing the quality of the included studies (Kappa statistic = 0.727). We also performed sensitivity analysis of only high-quality studies on AMH level of all patients, AMH level of different stage and pregnancy rate of patients. Its results shown that the two moderate studies did not influence the result obviously (shown in supplementary figure 2-4).

#### Characteristics of the included studies

**IBD and ovarian reserve.** Figure 2 showed the SMD of AMH level for total IBD patients in comparison with controls. The pooled SMD was -0.38 (95%CI: -0.67, -0.09) along with a significantly heterogeneity ( $I^2 = 79.0\%$ ;  $p = 0.000$ ). The pooled SMD for CD patients was -0.28 (95%CI: -0.61, 0.06); ( $I^2 = 75.4\%$ ;  $p = 0.003$ ), which is a little lower than that for UC patients (SMD = -0.14, 95%CI: -0.41, 0.12); ( $I^2 = 0.0\%$ ;  $p = 0.425$ ). IBD patients in remission stage have a similar ovarian reserve to normal population (SMD = -0.10, 95%CI: -0.32, 0.12); ( $I^2 = 0.0\%$ ;  $p = 0.667$ ), while patients in active stage have a significantly impaired ovarian reserve (SMD = -1.30, 95%CI: -1.64, -0.96); ( $I^2 = 0.0\%$ ;  $p = 0.318$ ), as shown in Figure 3. Subgroup analysis demonstrated that IBD patients under 30 years old have a relatively healthy ovarian reserve in comparison with control group (SMD = -0.56, 95%CI: -2.28, 1.16); ( $I^2 = 96.3\%$ ;  $p = 0.000$ ), and the condition deteriorates severely for IBD patients over 30 years old (SMD = -0.75, 95%CI: -1.07, -0.43); ( $I^2 = 0.0\%$ ;  $p = 0.608$ ), as shown in Figure 4. Few studies reported the basal antral follicle count (BAFC) of IBD patients. The pooled SMD for IBD patients is -0.03 (95%CI: -0.23, 0.18); ( $I^2 = 0.0\%$ ;  $p = 0.401$ ), both UC (SMD = -0.18, 95%CI: -0.44, 0.09); ( $I^2 = 0.0\%$ ;  $p = 0.522$ ) and CD (SMD = 0.22, 95%CI: -0.37, 0.82); ( $I^2 = 75.5\%$ ;  $p = 0.044$ ) patients seem to have similar BAFC with

healthy control as supplementary figure 1 demonstrated.

#### IBD and IVF outcomes

IBD patients were able to obtain a decent pregnancy rate after receiving IVF treatment. UC patients have a comparable pregnancy rate to normal women, while CD patients have lower pregnancy rate. Figure 5 showed the OR of pregnancy rate for total IBD patients in comparison with controls. The pooled OR was 0.87 (95%CI: 0.55, 1.37) along with a significant heterogeneity ( $I^2 = 70.1\%$ ,  $p = 0.035$ ). The pooled OR for CD patients was 0.62 (95%CI: 0.50, 0.76); ( $I^2 = 0.0\%$ ,  $p = 0.331$ ), which is a little lower than that for UC patients (OR = 0.99, 95%CI: 0.62, 1.59); ( $I^2 = 66.7\%$ ,  $p = 0.050$ ).

IBD patients could also obtain a decent live birth rate after receiving IVF treatment. Live birth was found to be less likely in women with CD but not in UC patients. Figure 6 showed the OR of live birth rate for total IBD patients in comparison with controls. The pooled OR was 0.81 (95%CI: 0.62, 1.06) along with a significant low heterogeneity ( $I^2 = 32.1\%$ ,  $p = 0.230$ ). OR for CD patients was 0.59 (95%CI: 0.37, 0.94); ( $I^2 = 27.0\%$ ,  $p = 0.242$ ), which was a little lower than that for UC patients (OR = 0.84, 95%CI: 0.71, 1.00); ( $I^2 = 6.5\%$ ,  $p = 0.343$ ).

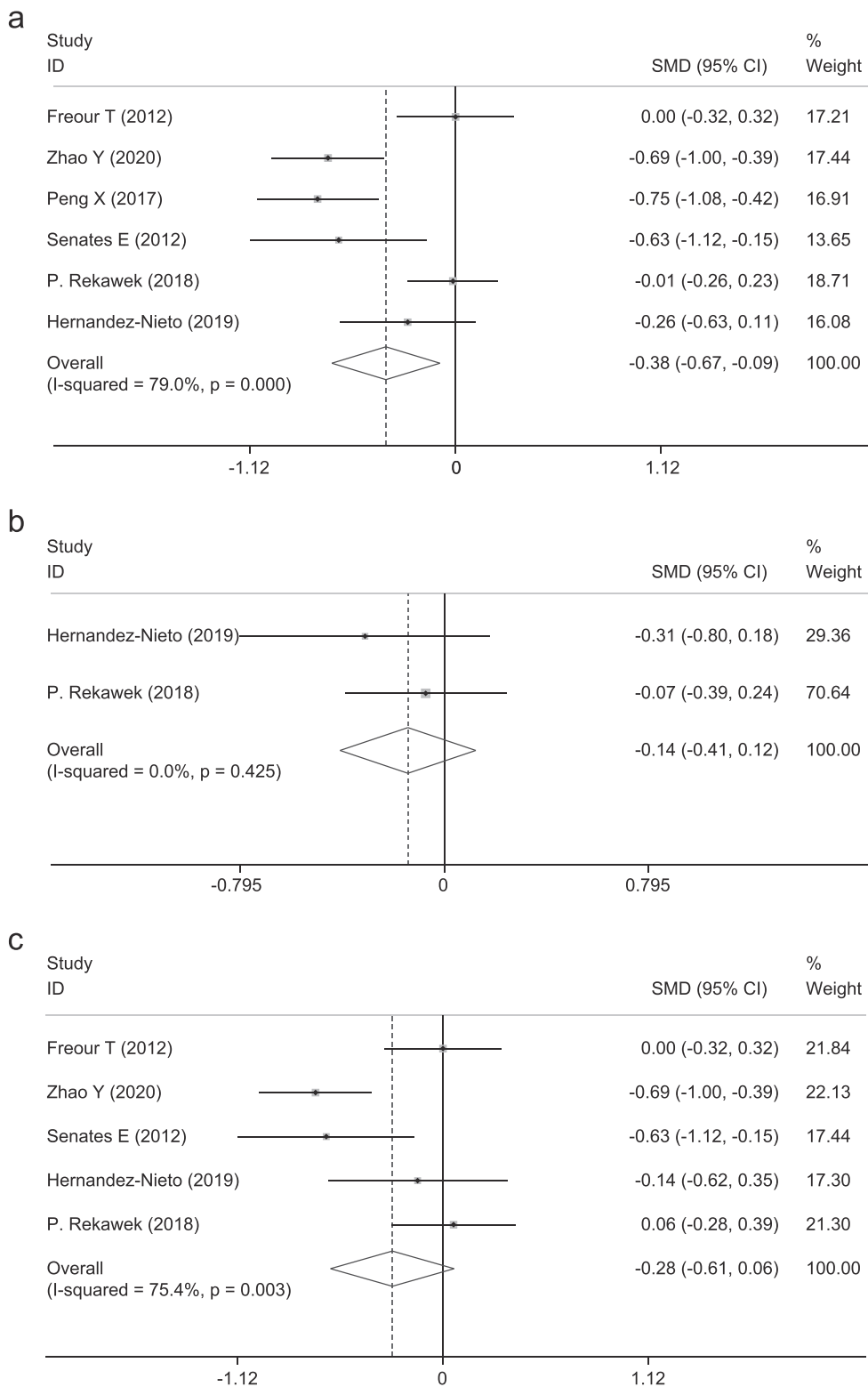
#### Discussion

This systematic review and meta-analysis included 9 studies with 2386 IBD records and 149742 records of matched controls. A conclusion was drawn from the analysis that IBD may be a risk factor for impaired ovarian reserve. The influence of IBD on the ovarian reserve changes with age and disease state. IBD patients can benefit from IVF and receive almost similar pregnancy rates and live birth rates to age-matched healthy population. A comprehensive search strategy was applied, and several databases were searched. There was no language restriction. To minimize the risk of bias, only high-quality (obtaining  $\geq 70\%$  of the highest score) and moderate-quality (obtaining 40–70% of the highest score) articles were included.

AMH is secreted by granulosa cells in women of reproductive age. AMH is absent in primordial follicles but is widely found in primary follicles, expressed most abundantly in the secondary, preantral and small antral follicles.<sup>26</sup> Thus, the AMH level is directly proportional to the number of secondary follicles, reflecting the residual follicular pool, and is the best parameter for predicting ovarian reserve.<sup>27,28</sup>

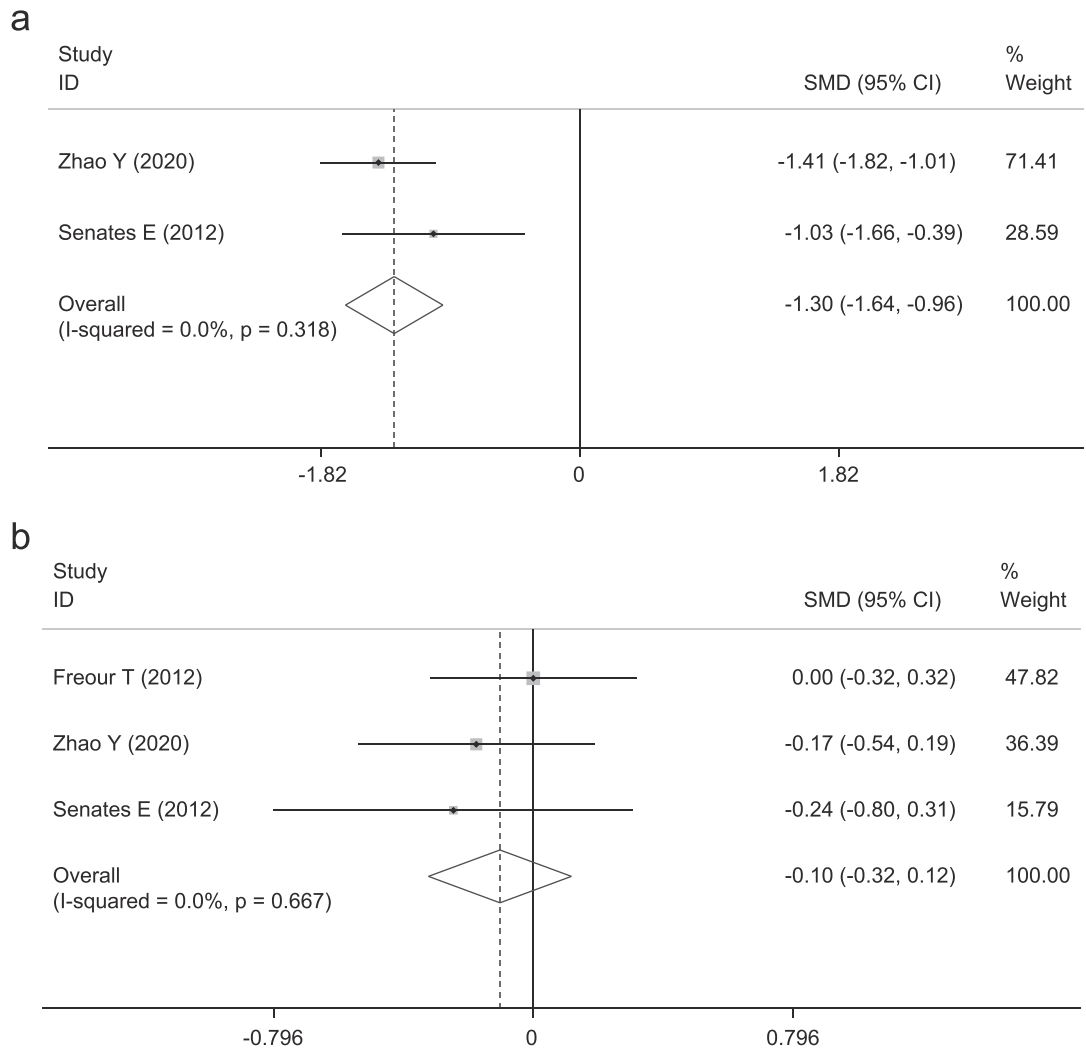
Autoimmunity has been reported to be deleterious to ovarian reserve, and is responsible for up to 40% of premature ovarian failure.<sup>29</sup> Ovaries are usually affected in both organ-specific and systemic autoimmune diseases.

Figure 2



**Figure 2.** Standardized Mean Differences of AMH level for patients with IBD in comparison with controls a: IBD patients; b: UC patients; c: CD patients. SMD= standardized mean difference, CI= confidence interval.





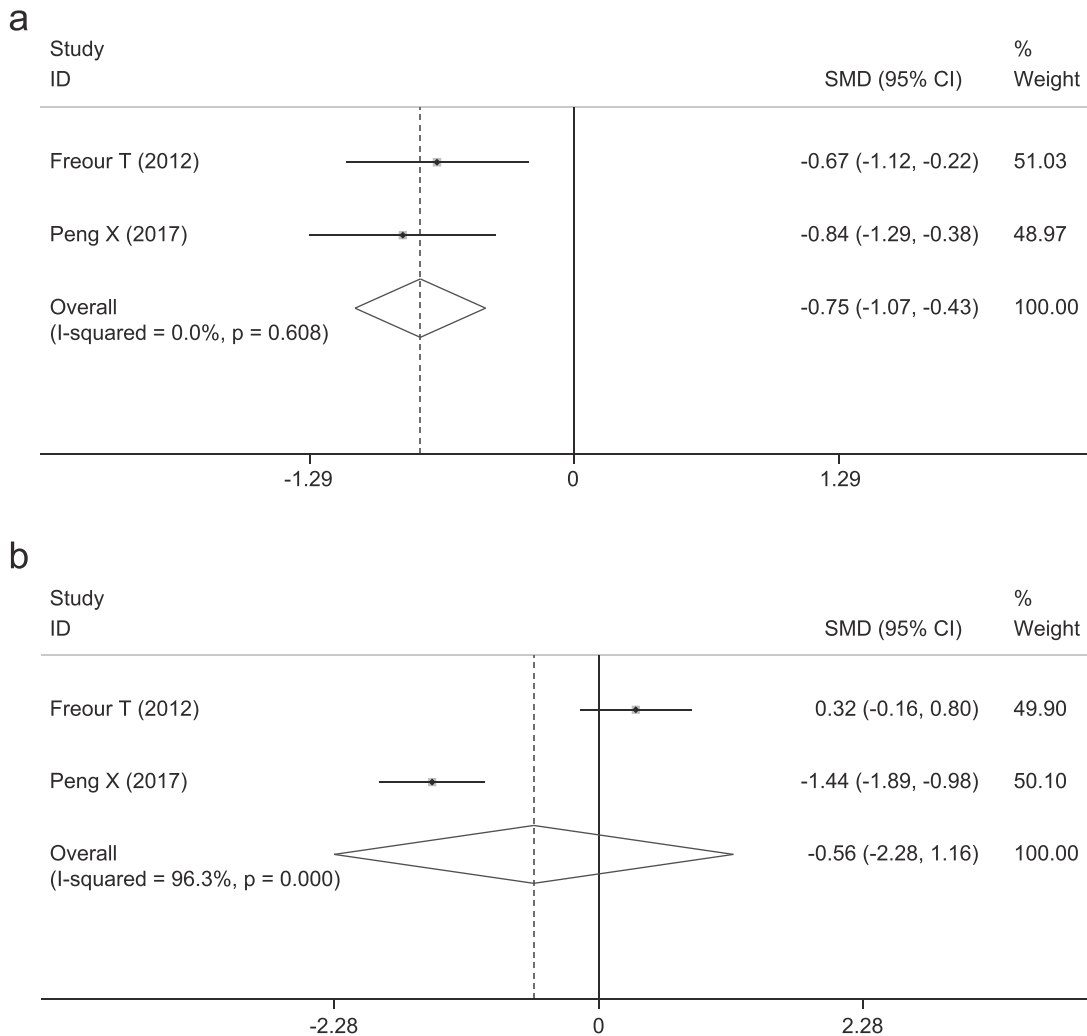
**Figure 3.** Standardized Mean Differences for AMH level for patients with IBD in different disease stage a: patients in active stage; b: patients in remission stage. SMD= standardized mean difference, CI= confidence interval.

IBD is a typical autoimmune disease with massive lymphocyte infiltration in the mucosa and disorder of antibodies.<sup>30</sup> Various autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis and primary antiphospholipid syndrome, were reported to negatively impact the ovarian reserve.<sup>30-34</sup> This relationship may be attributed to disorder of antibodies and antigens. In systemic lupus erythematosus patients, HLA-B27 positivity was associated with a significant reduction in AMH level.<sup>34</sup> A study found that 40.4% of all POF participants had at least one autoimmune disease.<sup>35</sup> IBD shares many characteristics with other autoimmune diseases. We speculate that antibody disorder and disrupted immune response may be responsible for the impaired ovarian reserve in IBD patients.

Furthermore, some drugs used in the treatment of IBD also have negative effects on ovarian reserve. It was

found that AMH levels and antral follicle counts (AFCs) in IBD patients not using thalidomide were lower than that of healthy people but higher than IBD patients taking thalidomide. This effect becomes more apparent when the treatment dose reached a certain extent, but is reversible after stop taking thalidomide for 3 months.<sup>22</sup> Recent research has found that when cyclophosphamide is administered to female mice, the number of primordial follicles was significantly reduced, causing premature ovarian insufficiency by dormant follicle activation.<sup>36</sup> Glucocorticoids were often used in moderate and severe patients in the active stage. When prednisone was applied in treatment of systemic lupus erythematosus, patients had smaller median ovarian volume.<sup>37</sup> It has been proved that both the IBD itself and the use of medicine were independent risk factors for lower ovarian reserve.<sup>22</sup>

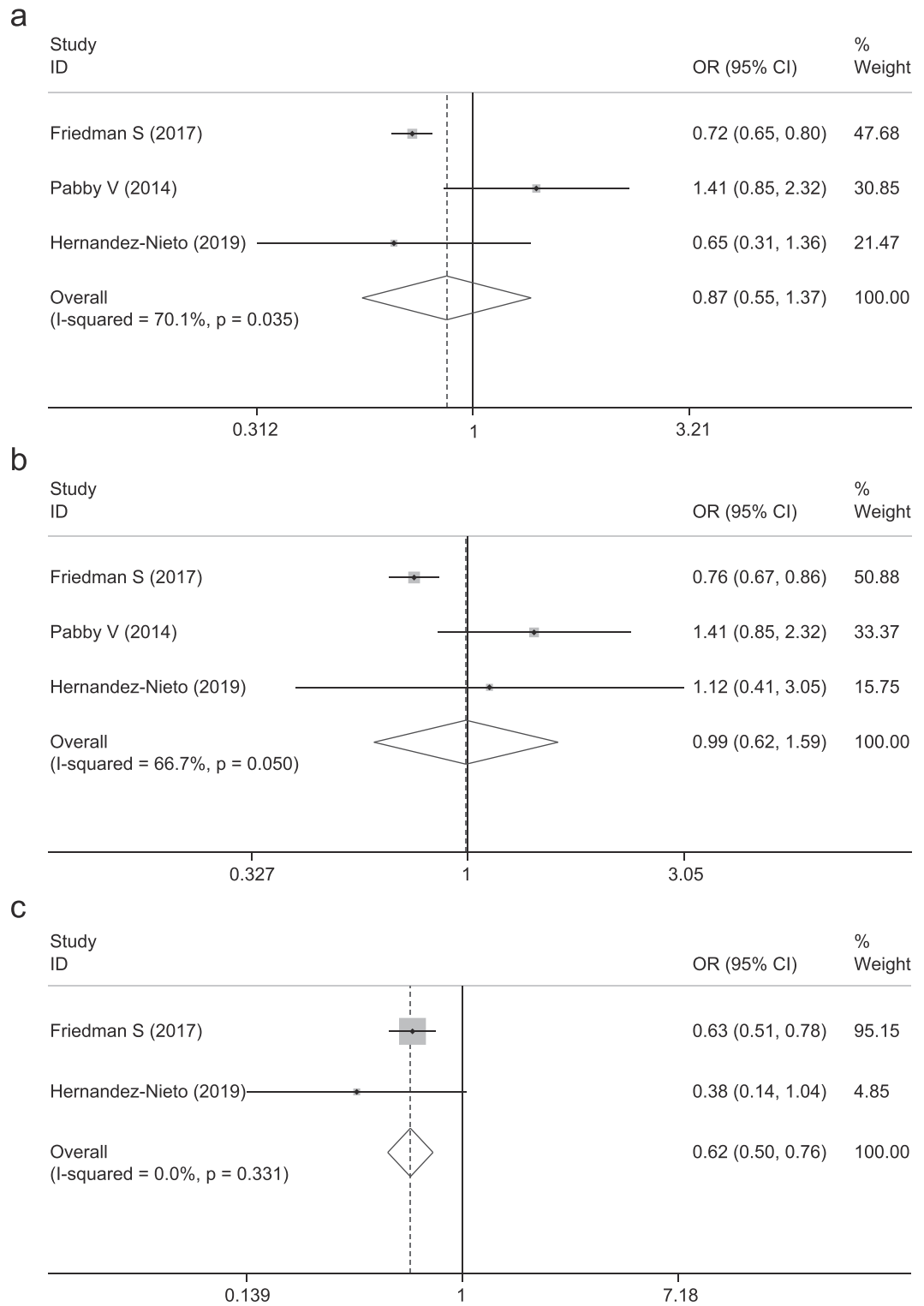




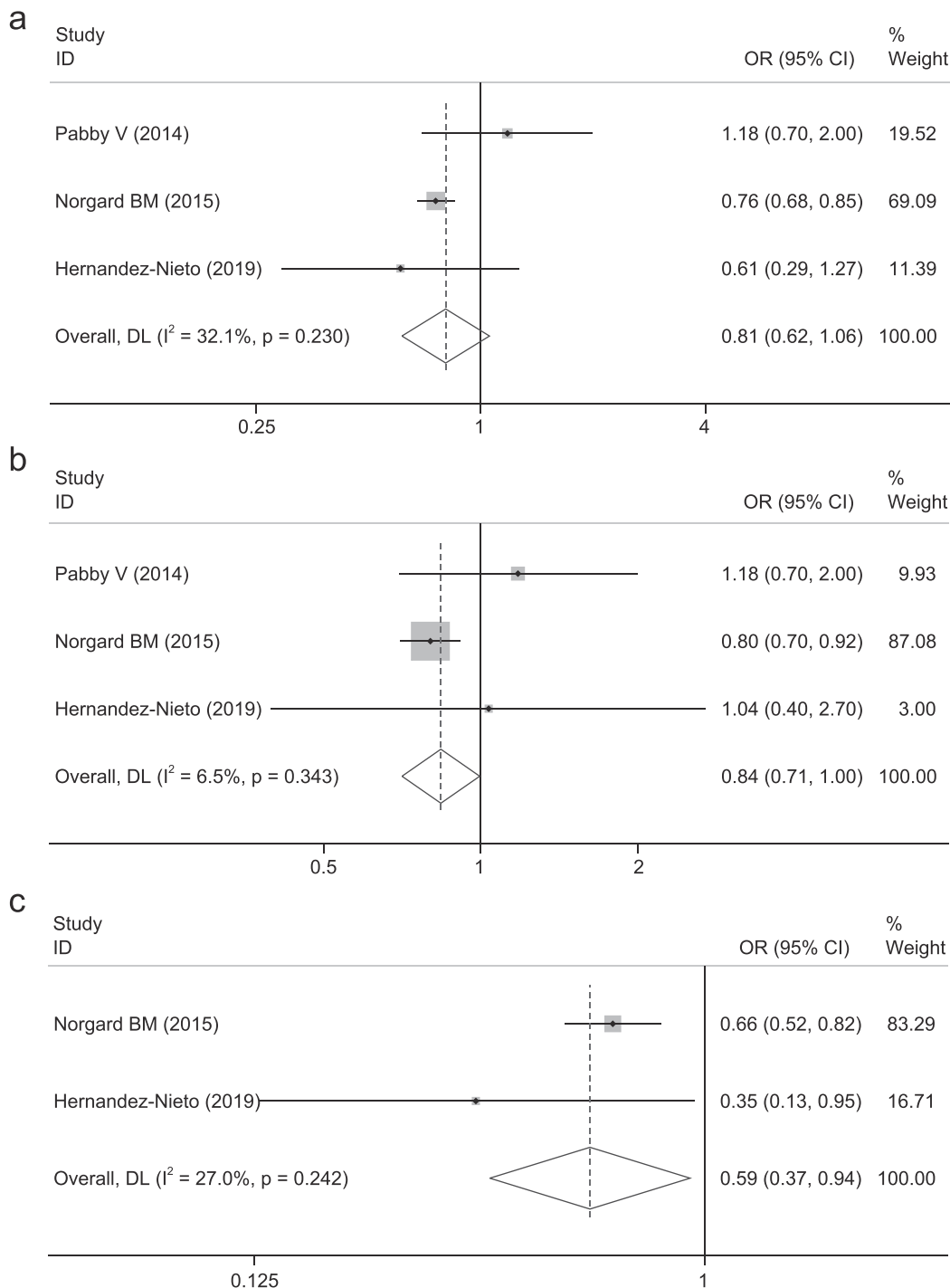
**Figure 4.** Standardized Mean Differences for AMH level of IBD patients of different age a: patients over 30; b: patients below 30. SMD= standardized mean difference, CI= confidence interval.

Malnutrition is one of the most prevalent systemic symptoms of IBD, which can be attributed to the following reasons: decreased oral intake, low absorption, increased nutrient requirements and increased gastrointestinal loss.<sup>38</sup> Its characteristics and severity were decided by affected region, duration and activity of the disease.<sup>39</sup> Malnutrition is a complex situation involving a series of nutrients deficiencies. For instance, the average serum folate concentration in IBD patients was significantly lower than that of control patients.<sup>40</sup> Previous studies have indicated that the prevalence of vitamin D deficiency in patients with IBD is higher.<sup>41</sup> Although the effect of vitamin D on female reproductive physiology remains controversial, a recent meta-analysis suggested that vitamin D supplementation could significantly alter serum AMH levels in ovulatory women without PCOS.<sup>42</sup>

Moreover, IBD influences various other aspects of the patients, resulting in further alteration of the ovarian reserve and reproductive function. For instance, surgical treatment was needed when complications such as gastrointestinal hemorrhage and intestinal perforation occurred. Abdominal surgery may lead to unclear influences on adjacent organs and the ovarian reserve. Several studies reported that the fertility of IBD women decreases sharply after receiving restorative proctocolectomy or ileal pouch-anal anastomosis (RP/IPAA).<sup>43-44</sup> Anemia is one of the major systemic symptoms of IBD, and recent evidence suggests that the mean AMH levels in women with sickle cell disease<sup>45</sup> and Fanconi anemia<sup>46</sup> are remarkably lower than those of the healthy population. It is well accepted that excellent ovarian function is related to good emotion and adequate rest. IBD is also more likely to trigger mental



**Figure 5.** Odds ratios of pregnancy rate for total patients with IBD in comparison with controls a: IBD patients; b: UC patients; c: CD patients. OR=odds ratio, CI= confidence interval.



**Figure 6.** Odds ratios of live birth rate for total patients with IBD in comparison with controls a: IBD patients; b: UC patients; c: CD patients. OR=odds ratio, CI= confidence interval.

health issues. A recent study highlighted the increased risk of psychological disorders in IBD patients, 97.4% patients had symptoms of anxiety, and 91% patients had symptoms of depression.<sup>47</sup> C57BL/6 mice showed a decreased number of preantral follicles and secondary

follicles, and shorter estrous phase after induced by chronic stress.<sup>48</sup>

Accordingly, an assumption could be made that the decrease of ovarian reserve in IBD patients results from multiple factors, including the disease itself and other

influences it caused, such as malnutrition, mental health issues, abdominal surgeries, use of medicine and so on.

A series of previous studies found that fertility was impaired in both UC and CD patients. The HR and 95% CI of the fertility rate was (0.88, 0.85-0.91) for CD and (0.96, 0.93-0.98) for UC in Sweden.<sup>49</sup> Another similar study in UK found that the live birth rate was 46.2 per 1000 person-years in women with IBD and 49.3 in women without IBD.<sup>50</sup> A meta-analysis conducted in 2013 found a 17-44% reduction in fertility in IBD females.<sup>4</sup> Moreover, both UC and CD women had an increased risk of spontaneous abortion.<sup>51</sup> Interestingly, in our study, we found that females with IBD undergoing IVF have comparable pregnancy outcomes with healthy women.

In clinical practice, most females with slightly decreased ovarian reserve still have a sharp response to exogenous gonadotropin and have comparable IVF outcomes with normal females. Based on our results mentioned above, we hypothesized that the decreased fertility of IBD females might be partially attributed to the impaired ovarian reserve. The application of controlled ovarian hyperstimulation may eliminate the negative effect of IBD on pregnancy outcomes. Other possible reasons for the decreased fertility rate in IBD women include sexual dysfunction. Sexual dysfunction rates were higher in IBD females, affecting about 53.6% IBD women.<sup>6</sup> Assisted reproductive technology is also efficacious for infertility caused by sexual dysfunction. IBD itself and its treatments might lead to unclear influence on anatomic structure of the abdominal and pelvic cavity. The risk of infertility showed a threefold increase after receiving IPAA, 50.1% of post-IPAA women were reported to be infertile.<sup>52</sup> Those alterations may result from anatomic changes in the uterine-fallopian tube relationship. In half of the post-IPAA cases, the fallopian tubes were adherent to the bottom of the lesser pelvis, and unilateral or bilateral occlusion was found in more than half of post-IPAA cases.<sup>53</sup> IVF is a viable treatment option for women with tubal infertility. Therefore, it may provide new evidence for similar IVF outcomes in IBD females compared to the general population.

AMH is the best marker to reflect the decline of reproductive capacity with age.<sup>54</sup> It is generally acknowledged that ovarian reserve decreases over time in reproductive-age women. A negative correlation between AMH levels and age could be observed between age 25 and menopause.<sup>55</sup> According to this research, IBD would damage ovarian reserve of reproductive age women, but the influence is more apparent in females over 30. IBD women under 30 were found to have a nearly equivalent ovarian reserve to age-matched healthy controls, but IBD women over 30 showed lower AMH levels than healthy controls of the same age.

This phenomenon could be explained from various aspects. Patients usually see the onset of IBD in their 20s, and the longer the disease exists, the more severe impact it will bring about. Patients with longer disease course may receive more treatments, including surgery and medical treatments. As we have discussed above, some drugs and operations for the treatment of IBD may negatively affect the ovaries. Furthermore, IBD patients with a longer disease duration may have worse nutrition status, higher risk of psychological disorders and decreased quality of life. As previously stated, all those elements were risk factors for impaired ovarian reserve.

Although both kinds of IBD affect ovarian reserve and fertility, the extent and mode of their influences are different. The result of our study showed that UC patients have a comparable pregnancy rate with normal women after IVF, while CD patients have a lower pregnancy rate. Previous researches support these conclusions, some authors suggested that CD might directly damage fertility by causing inflammation in the fallopian tubes and ovaries.<sup>56</sup> Other researchers also reported that CD is more likely to cause poor pregnancy outcomes than UC.<sup>57</sup> UC and CD share many characteristics but still differ in the lesion site, age of onset and influence on digestive function. For instance, the average serum folate concentration in UC but not CD patients is significantly lower than that in controls.<sup>40</sup> The prevalent view is that CD, especially active CD, would damage female fertility more apparently.<sup>56</sup> Conclusion of this research is accordant with previous studies, we found that CD would cause more severe damage on both pregnancy rate and live birth rate than UC.

Previous studies found that women with inactive IBD did not show obviously decreased capacity in fertility. Diminished fertility mainly appears during active stage but not remission stage.<sup>58</sup> Active IBD is associated with a higher risk of adverse pregnancy outcomes, including low birth weight, preterm birth, and spontaneous abortion. The quiescent disease would not add to their risk.<sup>51</sup> The result of our study is consistent with previous studies, indicating that ovarian reserve was severely damaged during the active stage of IBD, but IBD females in the remission stage have an equivalent ovarian reserve to the control population. The impaired ovarian reserve may eventually result in diminished fertility. The aggravated disease itself, impaired nutrients absorption, increased dose of medicine and decreased quality of life are all reasons for the worsening of the ovarian reserve in the active stage.

To our knowledge, this study is the first systematic review and meta-analysis to evaluate the influence of IBD on ovarian reserve and the pregnancy outcomes of IBD females.

Similar to all systematic reviews and meta-analyses on observational studies, the quality of our study is limited by the quality and heterogeneity of the included

studies. The heterogeneity is mainly attributed to the included studies' different geographical locations, races, and IVF protocols. Although, almost all of the studies controlled important variables such as age and BMI. Adjusted ORs or SMDs were not available in most of these studies; therefore, we could not conduct the meta-analysis on adjusted ORs or SMDs to reduce the influence of other confounding factors. The current analysis needs more studies to perform subgroup analysis, for instance, only 3 studies were available for the subgroup analysis of the live birth rate of the UC and CD patients separately. More research is needed to investigate further the effect of UC and CD on ovarian reserve and evaluate whether IVF treatment is helpful for IBD females.

The results of this study indicate that IBD may reduce reproductive age women's ovarian reserve. This influence results from the combined effect of two aspects: the direct influence of the immune response caused by the disease and the indirect influence, including using of anti-IBD drugs, nutrient deficiency, psychological disorders, and decreased quality of life. IBD do not affect ovarian reserve significantly before the age of 30 but significantly reduce the ovarian reserve after 30. IBD patients in the remission stage have comparable ovarian reserves to healthy individuals, while women in the active stage have severely diminished AMH levels. A systematic evaluation and a comprehensive therapy should be applied to balance fertility and disease control for IBD females who plan to conceive a child in the near future. Decisions should be made based on a consultation with obstetricians—gynecologists, gastroenterologists, and pediatricians. Females suffering from IBD should be advised to conceive a child during remission stage and before their 30s if the conditions allow, and drugs that potentially hazardous to the ovarian reserve or the reproductive function should be avoided or used with caution during pregnancy preparation. Surgical treatment should also be performed with caution, as former studies have proved that surgical managements such as IPAA will triple the risk of infertility compared to medical management.<sup>52</sup> IVF may be helpful to improve the pregnancy outcomes of IBD females, especially for those who have received surgical treatment.

#### Contributors

SHH and SH performed systematic search, SHH, WXX, SH, LD, LQ, BJS selected the included articles, WXX and LD collected all the data. SHH, TF, XRM did the statistical work, SHH and JJ drafted the manuscript. LD drawn the figures and tables, and revised the manuscript. All authors agreed on drafts of the paper. All authors confirmed that they had full access to all the data in the study and accepted responsibility to submit for publication.

#### Data sharing statement

The datasets generated for this study are available on request to the corresponding author.

#### Declaration of interests

None.

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#### Supplementary materials

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