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# HIGH FREQUENCY OF DEEP INFILTRATING ENDOMETRIOSIS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A NESTED CASE-CONTROL STUDY

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**Key Words:** IBD; endometriosis; deep infiltrating endometriosis

## ABSTRACT

**Introduction.** Inflammatory Bowel Disease (IBD) and endometriosis are chronic inflammatory diseases occurring in young women, sharing some clinical manifestations. In a multidisciplinary approach, we aimed to investigate symptoms, type and site of pelvic endometriosis in IBD patients versus non-IBD Controls with endometriosis.

**Methods.** In a prospective nested, case-control study, all female premenopausal IBD patients showing symptoms compatible with endometriosis were enrolled. Patients were referred to dedicated gynecologists for assessing pelvic endometriosis by transvaginal sonography (TVS). Each IBD patient with endometriosis (Cases) was

retrospectively matched for age ( $\pm 5$  years) and body mass index ( $\pm 1$ ) with 4 patients with endometriosis at TVS, but no-IBD (Controls). Data were expressed as median [range], the Mann-Whitney or Student-t and  $\chi^2$  tests were used for comparisons. **Results.** Endometriosis was diagnosed in 25 (71%) out of 35 IBD patients with compatible symptoms including 12 (52.6%) Crohn's Disease and 13 (47.4%) Ulcerative Colitis patients. Dyspareunia and dyschezia were significantly more frequent in Cases vs Controls (25 [73.7%] vs 26 [45.6%];  $p=0.03$ ). At TVS, deep infiltrating endometriosis (DIE) and posterior adenomyosis were significantly more frequently observed in Cases vs Controls (25 [100%] vs 80 [80%];  $p=0.03$  and (19 [76%] vs 48 [48%];  $p=0.02$ ). **Conclusions.** Endometriosis was detected in two-thirds of IBD patients with compatible symptoms. The frequency of DIE and posterior adenomyosis was higher in IBD than in Controls. A diagnosis of endometriosis, often mimicking IBD activity, should be considered in subgroups of female patients with IBD.

## Introduction

Inflammatory Bowel Disease (IBD) is characterized by a chronic relapsing course [1,2]. IBD include Crohn's Disease (CD) and Ulcerative Colitis (UC), sharing most symptoms and pathogenetic mechanisms, including a dysregulation of the mucosal immune response [3]. IBD may be associated with other dysimmune conditions mainly involving the skin, joints, eyes [4]. Intestinal symptoms represent the typical IBD-related manifestation, and chronic recurrent abdominal pain is typically observed in CD [1,2]. The occurrence of this relapsing symptom at young age may indeed suggest a diagnosis of CD.

Endometriosis is a chronic inflammatory disease affecting women in premenopausal age [5]. Differently from IBD, endometriosis is rather common, affecting approximately 10% of young women [6]. The etiology of endometriosis is still an open issue. However, as for IBD, a dysregulation of the host immune response has been suggested [7,8].

Signs and symptoms related to endometriosis are heterogeneous and often do not allow a conclusive diagnosis. Dysmenorrhea, dyspareunia, dyschezia, chronic pelvic and abdominal pain are more frequently observed [5,6]. Endometriosis has been associated with a broad spectrum of autoimmune diseases [7-10]. However, the association between endometriosis and IBD has been less extensively investigated. A large Danish cohort study reported that patients with endometriosis bear a higher risk of developing IBD [11]. The few available data regarding features of IBD in patients with concomitant endometriosis only suggest a higher risk of stricturing CD in these patients [9-12]. Conversely, characteristics of endometriosis in patients with concomitant IBD are currently undefined. Symptoms related to endometriosis may mimic those observed in IBD, particularly recurrent abdominal pain. This suggests that IBD-dedicated gastroenterologists should search for endometriosis in selected IBD patients with compatible symptoms, thus increasing the diagnostic yield of this potentially invalidating condition.

The diagnosis of endometriosis may therefore be underestimated or delayed in IBD, even during IBD-related surgery. Thus, a noninvasive diagnosis using transvaginal sonography (TVS) by dedicated gynecologists may be very useful. TVS, in experienced hands, shows a high accuracy in diagnosing endometriotic pelvic lesions [13-17]. The recent European Society of Human Reproduction and Embryology guidelines indeed recognized TVS as a valid tool for diagnosing endometriosis without the need of laparoscopic or histological confirmation [18].

On the basis of these observations, the aim of the present nested case-control study was to investigate in a multidisciplinary approach, symptoms, type and site of pelvic endometriosis in patients with or without IBD.

## Materials and methods

### Study protocol

From May 2020 to March 2022, consecutive female IBD patients in premenopausal age referring symptoms compatible with endometriosis or with a referred diagnosis of endometriosis were prospectively enrolled. All the enrolled patients were under follow-up at the IBD referral center of the “Tor Vergata” University Hospital of Rome (Italy). Diagnosis of IBD was based according to standard criteria and characteristics defined according to the Montreal classification [19]. Symptoms compatible with endometriosis were searched by gastroenterologists during routine IBD-dedicated visits, including: dysmenorrhea, dyschezia, dyspareunia, dysuria, heavy menstrual bleeding (HMB), chronic abdominal pain.

All the enrolled patients were assessed, after written informed consent, by TVS at the Gynecological Ultrasound Unit of the “Tor Vergata” University Hospital of Rome. TVS was performed in order to search, diagnose, characterize or confirm the diagnosis of pelvic endometriosis.

After TVS, for each IBD patient with concomitant endometriosis (Cases), 4 patients with a diagnosis of endometriosis without IBD (Controls) were matched for age ( $\pm 5$  years) and BMI ( $\pm 1$  Kg/m<sup>2</sup>). At this purpose, the electronic database of the above reported Gynecological Ultrasound Unit was used.

### Study population

Inclusion criteria for Cases were: a) well-defined diagnosis of IBD [20,21]; b) premenopausal women age  $>16$  and  $\leq 55$  years; c) follow-up ( $\geq 2$  visit/year) at the reported IBD center; d) sign and symptoms compatible with endometriosis (dysmenorrhea, dyschezia, dyspareunia, dysuria, HMB and/or chronic abdominal pain) or referred diagnosis of endometriosis; e) written informed consent to be enrolled and assessed by TVS. Exclusion criteria were: a) missing/incomplete data; b) severe comorbidities; c) menopause; d) pregnancy; e) ultrasound suspicion of malignancy of pelvic organs.

Inclusion criteria for Controls were: a) well-defined diagnosis of endometriosis at TVS; b) detailed demographic and clinical history; c) written informed consent to collect and report anonymised personal data and TVS reports for research purposes. Exclusion criteria were: a) missing/incomplete clinical and TVS data; b) menopause; c) defined or suspected diagnosis of IBD.

### Clinical assessment of intestinal symptoms

Demographic and clinical characteristics of each patient were prospectively reported in a database including: birth date, BMI, IBD duration, IBD type, UC extent [19], CD location and behavior [19], previous/ongoing treatment with thiopurines, methotrexate or biologics, smoking status, IBD-related surgery, endometriosis-related surgery. Symptoms compatible with endometriosis were searched, including: dysmenorrhea, dyschezia, dyspareunia, dysuria, HMB, chronic abdominal pain.

## Clinical assessment of gynecological symptoms

A detailed medical, surgical, and obstetrical/gynecological history (age, BMI, age at menarche, gravidity, parity, infertility, menstrual cycle characteristics, last menstrual period, previous surgery and familial metabolic, oncological diseases) was recorded.

Symptoms compatible with endometriosis and adenomyosis were recorded for both Cases and Controls: dysmenorrhea, dyspareunia, dyschezia, dysuria, HMB. The pain severity was evaluated with the visuo-analogue scale (VAS), using a 10 cm line: from 0 (no pain) to 10 (maximum pain). Pain was considered significant for a VAS score  $\geq 5$ . HMB was assessed by patients, reputed reliable and comparable to the pictorial blood loss analysis chart score [22,23]. Infertility was defined as no pregnancy after 12 months of intercourses. Any ongoing medication was recorded. Patients using contraceptives were asked to report all characteristics of symptoms before treatment.

## Transvaginal Ultrasound examination

The Ultrasound (US) examination was performed using a Voluson E6, E8, or E10 device (GE Healthcare; Zipf, Austria) using transvaginal (5.0 - 9.0 MHz) probes. A conventional transvaginal two-dimensional (2D) ultrasound with greyscale and power/color Doppler was performed to assess the pelvis.

Endometriomas, pelvic adhesion, deep infiltrating endometriosis (DIE) and adenomyosis were recorded according to current classifications [17,24].

The scan examined the uterus, adnexa, the pouch of Douglas, other pelvic organs (bladder, ureters, rectum, rectosigmoid junction) and sites (posterior/lateral/anterior parametria, rectovaginal septum, vesico-uterine pouch, uterosacral ligaments). Ovarian endometrioma was diagnosed by US in case of a persistent uni/multilocular cyst showing a homogeneous low-level echogenicity of the fluid and absent or moderate vascularization [17]. DIE was diagnosed according to validated ultrasonographic criteria [17,23,24]:  $\geq 1$  structure in the anterior or posterior compartment with abnormal retroperitoneal hypoechoic linear or nodular thickening, irregular contours and no or few Doppler signals. Sonographic uterine adenomyosis findings were recorded [26]. Adenomyosis was diagnosed in case of  $\geq 2$  of the following: myometrial cystic areas, hyperechoic islands, linear striations, buds or irregular/infiltrated endometrial-myometrial junction zone [17,24-28]. The location of adenomyosis of the uterus was recorded (anterior, lateral and posterior uterine walls). Scan was performed using a US mapping system [17,23,26,28]. Adhesions without other US findings of endometriosis were not considered diagnostic for endometriosis.

## Ethical considerations

The study protocol was approved by the independent Ethic Committee of the University Hospital "Tor Vergata" of Rome, Italy (protocol n 126/20). All the enrolled patients gave their written informed consent to participate to the study and to undergo TVS. Non-IBD patients with endometriosis were asked, by the referral Gynecologists, for consent to process their personal anonymised data for research purposes.

## Statistical analysis

Data were expressed as median [range]. Normal distribution of continuous variables was assessed and confirmed by the Kolmogorov-Smirnov test. Differences between qualitative and quantitative variables was assessed by  $\chi^2$  test, Mann-Whitney and Student's *t*-test, as appropriate. Statistical significance was considered for all variables if  $p < 0.05$ . Statistical analysis was performed with IBM-SPSS statistical software vers. 26.0.

## Results

### Study population

From May 2020 to March 2022, 35 IBD patients fulfilling the inclusion criteria were enrolled. After TVS, clear sonographic endometriosis signs were detected in 25 (71.4%) patients (Cases). Overall, the study population included 125 patients with endometriosis: 25 with concomitant IBD and 100 matched patients with no IBD. Table 1 summarizes clinical characteristics of the study population. When considering the entire population of 125 patients with endometriosis, the median age was 39 [22-53] years, with no difference between Cases and Controls (38 [25-53] vs 39 [22-52];  $p=0.49$ ). The age at diagnosis of endometriosis was higher in Cases vs Controls (38 [25-53] vs 30 [22-52];  $p=0.01$ ) (Table 1).

### Characteristics of endometriosis in Cases and Controls

Among endometriosis-related symptoms, dyschezia and dyspareunia were more frequently observed in Cases than in Controls (11 [44%] vs 17 [17%];  $p=0.008$  and 19 [76%] vs 51 [51%];  $p=0.04$ ). The frequency of other symptoms related to endometriosis did not differ between the two groups (Table 1).

DIE (Figure 1) was detected by TVS in all Cases (25 [100%]), and its frequency was significantly higher in Cases than in Controls (25 [100%] vs 80 [80%];  $p=0.03$ ). No differences were detected between Cases and Controls in terms of frequency of posterior DIE (21 [84%] vs 78 [78%];  $p=0.69$ ) or of frequency of rectosigmoid endometriosis (6 [24%] vs 25 [25%];  $p=0.87$ ). Bilateral ovarian endometriomas (Figure 2) were more frequently observed in Controls than in Cases (19 [19%] vs 0 [0%];  $p=0.03$ ). Differently, the proportion of patients with other localizations of endometriosis was comparable between groups (Table 1).

The frequency of adenomyosis (Figure 3) was comparable between Cases and Controls (19 [76%] vs 62 [62%];  $p=0.24$ ). However, when separately considering anterior, posterior and lateral adenomyosis, posterior adenomyosis was more frequent in Cases than in Controls (19 [76%] vs 48 [48%];  $p=0.02$ ) (Table 1).

In our population, adhesions detected by dynamic TVS examination were significantly more frequently observed in Cases than in Controls (24 [96%] vs 71 [71%];  $p=0.001$ ). However, since adhesion can be determined not only by the endometriotic pelvic disease but also by IBD itself and related surgery, this parameter was not considered specific for endometriosis.

### Clinical characteristics in IBD patients with endometriosis

Clinical characteristics of the 25 IBD patients with concomitant endometriosis are reported in Table 2. In IBD group, there were 13 (52%) UC and 12 (48%) CD patients. UC extent included proctitis in 3 (23%), left-sided colitis in 5 (38.5%) and pancolitis in 5 (38.5%) patients (Table 2). CD lesions involved the ileum in 4 (33.3%), the colon in 1 (8.4%) and the ileum-colon in 7 (58.3%) patients. CD behavior was non stricturing-non penetrating in 6 (50%), stricturing in 3 (25%) and penetrating in 3 (25%) patients (Table 2).

### Endometriosis: symptoms and type in IBD

Fertility, gravidity and age at diagnosis of endometriosis were comparable between UC and CD ( $p=0.54$ ,  $p=0.56$  and  $p=0.8$ , respectively). In patients with assessable parity, no differences were detected between UC and CD (2/13 [15%] vs 3/12 [25%];  $p=0.54$ ). The proportion of patients with symptoms compatible with endometriosis was comparable between UC and CD (Table 3).

The frequency of posterior DIE and rectosigmoid endometriosis did not differ between UC and CD patients (11 [84.6%] vs 10 [83.3%];  $p=0.64$  and 2 [15.4%] vs 4 [33.3%];  $p=0.56$ , respectively). The proportion of patients with left utero-sacral ligament endometriosis was higher in UC than in CD (11 [84.6%] vs 4 [33.3%];  $p=0.02$ ), while the frequency of right utero-sacral ligament was comparable between UC and CD groups (1 [7.7%] vs 2 [16.6%];  $p=0.94$ ). The frequency of other endometriosis localizations did not differ between UC and CD (Table 3). A high frequency of adenomyosis, comparable between UC and CD (11 [84.6%] vs 8 [66.6%];  $p=0.56$ ), was observed.

### Treatment for endometriosis: responsiveness

After the diagnosis of endometriosis, 20 out of the 25 IBD patients received a long-term treatment with hormone therapy and 12 were followed-up for  $\geq 6$ -months. Treatment in these 12 patients included Dienogest (2 mg) in 7,

estroprogestins in 3, progestin-releasing intrauterine device in 2. At 6-months, all these 12 patients showed clinical improvement in terms of both abdominal pain and of endometriosis-related symptoms. Hormone therapy determined iatrogenic amenorrhea, therefore no patients reported dysmenorrhea after treatment. Before treatment, all these 12 IBD patients showed a VAS score  $\geq 5$  for dyspareunia, while after 6-months treatment, only 3 out of 12 reported a VAS score  $\geq 5$ . Regarding dyschezia, 11 out of these 12 patients had a VAS  $\geq 5$  at baseline, while after 6-months treatment, this symptom persisted only in 2 out of these patients.

## Discussion

IBD and endometriosis share some clinical features, including the relapsing course and the onset at young age. Chronic abdominal pain, diarrhea and rectal bleeding may also occur in both conditions [1,2,5]. Thus, the differential diagnosis between IBD and endometriosis may be challenging, even for expert clinicians. Diagnosing endometriosis in patients with a previous diagnosis of IBD may show even more difficulties. This is particularly true for CD, characterized by recurrent abdominal pain, most often occurring at young age, as also observed in patients with endometriosis [1]. An inaccurate search for sign/symptoms of endometriosis may lead to a missed or delayed diagnosis, and therefore treatment, of this condition. Moreover, in patients with a well-defined diagnosis of CD or UC, a missed diagnosis of endometriosis may be responsible for an inappropriate and unsuccessful overtreatment for IBD. Beside symptoms shared by these two conditions, technical difficulties in diagnosing endometriosis, previously requiring invasive surgery with histology, may also reduce the diagnostic rate of endometriosis. In recent years, TVS has become a valid and accurate noninvasive tool for assessing pelvic endometriosis. This technique is currently recognized as a valid diagnostic modality, without the need of surgery and histology [18]. Therefore, a noninvasive diagnostic assessment of endometriosis in IBD is a relevant clinical issue, potentially avoiding useless and/or harmful treatments.

By our knowledge, evidences regarding the possible association between IBD and characteristics of concomitant endometriosis are currently lacking. In the present study, we therefore aimed to investigate the association between IBD and endometriosis, as also possible differences in terms of characteristics, type and sites of endometriotic lesions in matched patients with or without IBD.

Overall, symptomatic endometriosis searched by IBD-dedicated gastroenterologists and gynecologists was diagnosed in more than two thirds of IBD patients (71.4%). This observation suggests the need to consider a diagnosis of endometriosis in IBD patients with demographic and clinical features compatible with this condition.

In patients with endometriosis, dyschezia and dyspareunia were significantly more frequently observed in IBD patients than in Controls. Dyschezia is one of the typical but not specific symptoms associated with endometriosis [5], but it is also frequently observed in colorectal IBD. Therefore, the occurrence of this symptom in female IBD patients in premenopausal age should suggest a possible diagnosis of endometriosis, particularly in refractory patients. This finding also suggests that additional symptoms, beside dysmenorrhea, should be searched in order to consider a diagnosis of endometriosis in IBD. In our study population, dyspareunia was significantly more frequent in IBD patients than in Controls ( $p=0.04$ ). This peculiar symptom is also often not specifically searched by dedicated gastroenterologists during clinical assessments for IBD.

Among the most relevant findings, TVS detected DIE in a significantly higher proportion of patients with IBD than non-IBD ( $p=0.03$ ). Diagnosing DIE by TVS is more difficult than ovarian endometriosis, thus strongly supporting the need of dedicated gynecologists for a proper sonographic diagnosis. Interestingly, the frequency of posterior adenomyosis detected by TVS was significantly higher in patients with IBD than in Controls. A high frequency of posterior DIE and utero-sacral ligament was also observed in IBD. These endometriotic locations in the posterior pelvis, may determine symptoms mimicking IBD-related abdominal pain and even worsen intestinal symptoms and/or dyspareunia.

In our series, the median age at diagnosis of endometriosis was significantly higher in patients with IBD than in non-IBD. The observed difference between Cases and Controls in terms of median age at diagnosis of endometriosis may suggest a possible delayed diagnosis of endometriosis in IBD. Potential overlap in terms of symptoms related to the two conditions may be hypothesized for this finding. Clinical assessments mainly focused on intestinal symptoms during routine visits for IBD, even when performed by dedicated gastroenterologists, may also be involved.

The observed higher frequency of posterior endometriosis in the tested population ( $p=0.04$ ) further supports that diagnosing endometriosis in IBD patients requires not only the search for specific symptoms, but also the assessment by dedicated gynecologists. Colonoscopy is often performed in IBD patients, but this technique most often cannot visualize endometriosis. This is particularly true in case of DIE, condition requiring gynecological TVS or pelvic Magnetic Resonance Imaging for appropriate diagnosis [18]. Overall, the reported observations suggest that, in IBD patients, endometriosis needs to be searched in tertiary referral centers dedicated to IBD and endometriosis.



Among limitations of the present study, despite the quite high overall number of tested patients with endometriosis (n=125), the subgroup of IBD patients with concomitant endometriosis was relatively small (n=25). However, evidences regarding the association between IBD and endometriosis is, by our knowledge, very limited. The focus on endometriosis characteristics, assessed by dedicated gynecologists, appears as the major strength of our study. The study population, including a homogeneous cohort of patients with IBD and/or endometriosis followed-up at tertiary referral centers, adds support to the reliability of the findings. The same is true for the methodology used for detecting and classifying endometriosis, performed by dedicated specialists from the same Gynecological Unit. Moreover, the prospective enrollment of IBD patients with symptoms compatible with endometriosis and the nested case-control study design, should lower the risk for selection bias, thus allowing appropriate comparisons between groups.

In conclusion, in our nested case-control study, endometriosis was detected in more than two-thirds of IBD patients, with a high rate of DIE and posterior adenomyosis. Symptoms related to endometriosis, particularly DIE, may partially overlap those observed in patients with IBD. The observed higher frequency of dyspareunia and dyschezia in patients with IBD and concomitant endometriosis suggests the need to search for these symptoms for a differential or concomitant diagnosis in young female patients with recurrent abdominal pain.

A multidisciplinary approach including gastroenterologists and gynecologists experts in the field may increase the diagnostic rate, the characterization and treatment of endometriosis in IBD. The reported observations suggest that endometriosis should be considered as a potential confounder in subgroups of IBD patients with compatible symptoms, often mimicking IBD activity. Present findings also suggest that, after a proper diagnosis and classification, combined treatment for both endometriosis and IBD may improve the clinical outcome of these patients, including recurrent refractory abdominal pain. Further research in this field may add new insights in clinical management of patients with IBD.

## STATEMENTS

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## Statement of Ethics

The study protocol was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the independent Ethic Committee of the University Hospital “Tor Vergata” of Rome, Italy (protocol n 126/20).

### **Consent to participate statement.**

All the enrolled patients gave their written informed consent to participate to the study and to undergo TVS. Non-IBD patients with endometriosis (Controls) were asked, by the referral Gynecologists, for consent to process their personal anonymised data for research purposes.

### **Conflict of Interests Statements**

The authors declare no conflict of interest related to the study. Biancone L: speaker fee from Takeda, Janssen, ViforPharma, Celltrion; Calabrese E: speaker fee from Takeda, Janssen, MSD.

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### **Author Contributions**

B.N., L.B. and C.E. were responsible for conceptualization of the study. B.N. and L.B. both equally wrote the main manuscript text. B.N., C.R., G.R., E.C., M.M., R.M., A.S. and F.G.M. were responsible for acquisition, data and patient recruitment. B.N. and C.R. were responsible for data and statistical analysis and manuscript preparation. L.B. and C.E. were responsible for manuscript reviewing.

### **Data availability Statement**

Further enquiries can be directed to the corresponding author.

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## LEGENDS FOR THE FIGURES

### Figure 1 (panels a,b)

Transvaginal ultrasound appearance of posterior deep infiltrating endometriosis (DIE) in a different Crohn's Disease (CD) patient: **Panel a.** DIE nodule of the rectum (yellow dot line 1) and DIE nodule of the retrocervical region involving the torus and the left utero sacral ligament (USL) (yellow dot line 2). Thickening of the bowel wall related to CD (white arrows) is observed, together with retraction of the intestinal loops, due to an endometriotic nodule (yellow arrows). **Panel b.** Typical DIE lesion of the rectum (yellow dot line 1), showing thickening of the muscular layer and curved retraction of the bowel wall.

### Figure 2 (panels a,b)

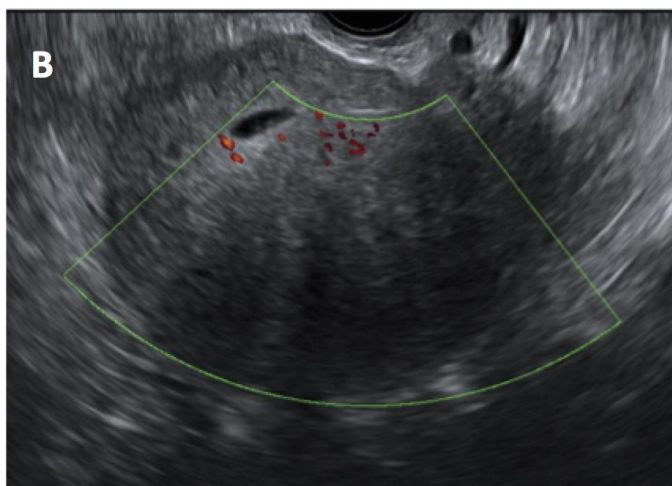
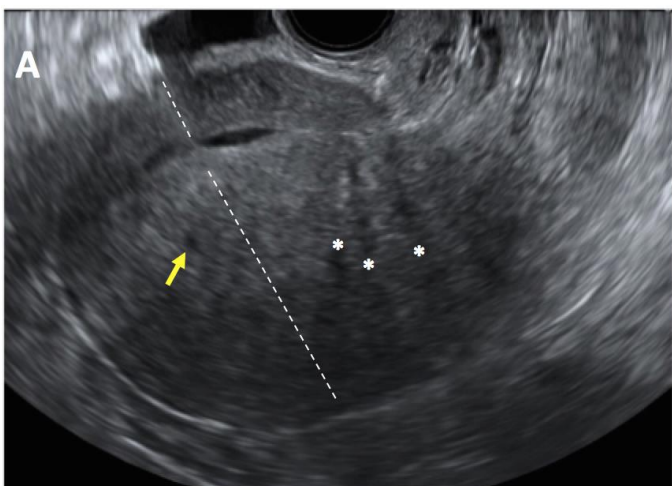
Transvaginal ultrasound appearance of an ovarian endometrioma in one Ulcerative Colitis (UC) patient. **Panel a.** Typical appearance of a persistent unilocular cyst with ground glass echogenicity. Normal multifollicular ovarian tissue around the cysts are visualized (white arrows). **Panel b.** The same endometrioma with power-Doppler shows the typical poor peripheral vascularization.

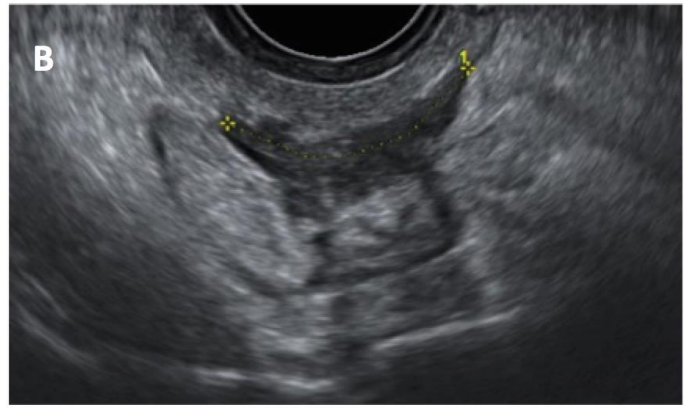
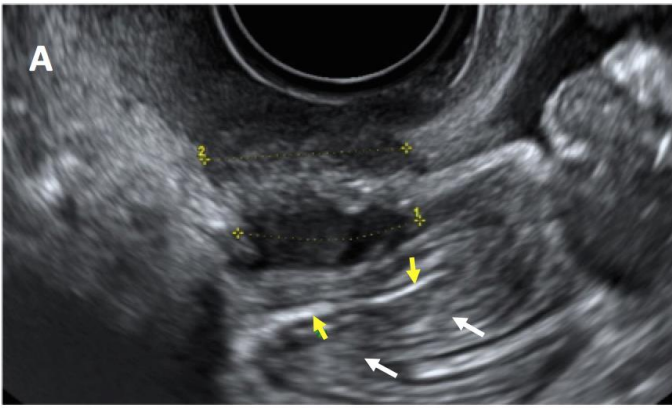
### Figure 3 (panels a,b)

Transvaginal ultrasound images from one patient with Crohn's Disease (CD): **Panel a.** Gray-scale image shows a globally enlarged uterus, asymmetrically thickening of the uterine walls (white dot lines) and abnormal myometrial echogenicity. Specific ultrasound signs of adenomyosis are observed in the posterior uterine wall, including small cystic anechoic areas surrounded by hyperechoic ring (yellow arrow) and linear myometrial fan-

shaped shadowing (yellow asterisks). **Panel b.** Power Doppler image of the same CD patient, showing adenomyosis in the posterior uterine wall, with diffusely spread vessels without a circular flow along a capsule, typical for leiomyoma.

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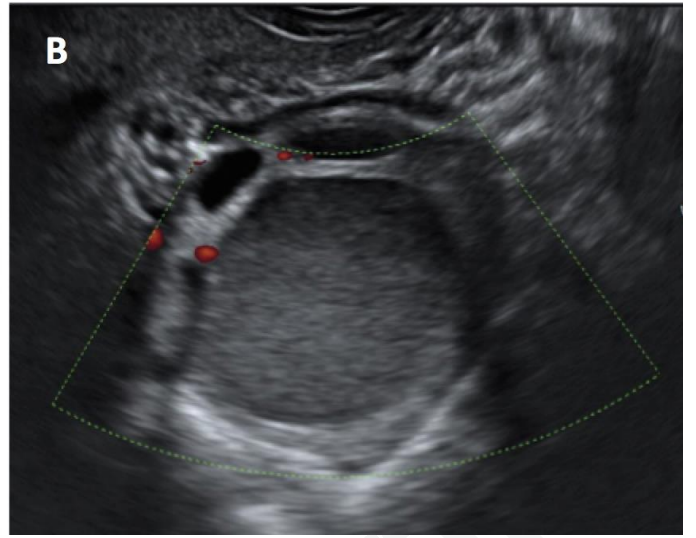
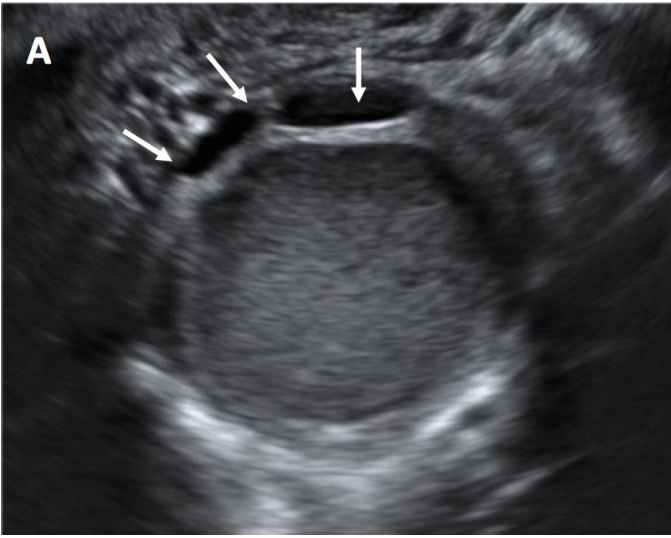




Table 1. Demographic and clinical characteristics of patients with endometriosis and with versus without IBD

	IBD (n=25)	No IBD (n=100)	p
Demographic characteristics	<i>median [range]</i>	<i>median [range]</i>	
Age	38 [25-53]	39 [22-52]	0.49
BMI	21.7 [17.3-41.6]	22.1 [18.3-41.4]	0.69
Menarche	12 [10-17]	12 [9-18]	0.07
Gravidity, n (%)	8 (32%)	54 (54%)	<b>0.08</b>
Age at diagnosis of endometriosis	38 [25-53]	30 [22-52]	<b>0.01</b>
Endometriosis-related symptoms	<i>n (%)</i>	<i>n (%)</i>	
Dysmenorrhea	22 (88%)	80 (80%)	0.52
Dyschezia	11 (44%)	17 (17%)	<b>0.008</b>
Dyspareunia	19 (76%)	51 (51%)	<b>0.04</b>
Dysuria	3 (12%)	6 (6%)	0.54
HMB	16 (64%)	56 (56%)	0.61
Infertility	7 (28%)	26 (26%)	0.95
Endometriosis Type	<i>n (%)</i>	<i>n (%)</i>	
DIE	25 (100%)	80 (80%)	<b>0.03</b>
Ovarian Endometriosis	12 (48%)	59 (59%)	0.37
Adhesions	24 (96%)	71 (71%)	<b>0.001</b>
Endometriosis pelvic sites	<i>n (%)</i>	<i>n (%)</i>	
Anterior DIE	0 (0%)	0 (0%)	n.a
Posterior DIE	21 (84%)	78 (78%)	0.69
Recto-sigma	6 (24%)	25 (25%)	0.87
RVS	2 (8%)	9 (9%)	0.81
Torus	5 (20%)	23 (23%)	0.95
Vagina	0 (0%)	0 (0%)	n.a
Lateral DIE	16 (64%)	73 (73%)	0.46
USL	15 (60%)	70 (70%)	0.33
Right USL	3 (12%)	32 (32%)	0.08
Left USL	15 (60%)	51 (51%)	0.56
Bilateral USL	3 (12%)	13 (13%)	0.84
Parametria	1 (2%)	4 (4%)	0.56
Endometrioma	12 (48%)	59 (59%)	0.37
Right endometrioma	6 (20%)	33 (33%)	0.53
Left endometrioma	6 (20%)	45 (45%)	0.09
Bilateral endometrioma	0 (0%)	19 (19%)	<b>0.03</b>
Salpinx	5 (20%)	8 (8%)	0.13
Right tube	3 (12%)	6 (6%)	0.45
Left tube	2 (8%)	2 (2%)	0.37
Bilateral tubes	2 (8%)	2 (2%)	0.37
Adenomyosis	19 (76%)	62 (62%)	0.24
Anterior adenomyosis	9 (36%)	45 (45%)	0.50
Posterior adenomyosis	19 (76%)	48 (48%)	<b>0.02</b>
Lateral adenomyosis	6 (20%)	19 (19%)	0.58

IBD: Inflammatory Bowel Disease; BMI: Body Mass Index; DIE: Deep Infiltrating Endometriosis; RSV: Recto-Vaginal Septum; USL: Utero-Sacral Ligament; HMB: Heavy Menstrual Bleeding.

Table 2. Clinical and demographic characteristics of Ulcerative Colitis and Crohn’s Disease in patients with endometriosis.

	IBD (n=25)	UC (n=13)	CD (n=12)	p
Demographic characteristics	median [range]	median [range]	median [range]	
Age	38 [25-53]	39 [25-53]	38 [28-47]	0.75
BMI	21.7 [17.3-41.6]	22.8 [17.3-29.6]	20.9 [18.7-41.6]	0.87
Menarche	12 [10-17]	12 [10-14]	12 [10-1]	0.98
Age at endometriosis diagnosis	38 [25-53]	38 [25-53]	37 [28-47]	0.8
Gravidity, n (%)	8 (32%)	2 (15%)	4 (33%)	0.56
IBD duration	11.5 [1-35]	11 [1-25]	12 [1-35]	0.8
IBD characteristics	n (%)	n (%)	n (%)	
UC extension				
E1	n.a.	3 (23%)	n.a.	n.a.
E2	n.a.	5 (38.5%)	n.a.	n.a.
E3	n.a.	5 (38.5%)	n.a.	n.a.
CD localization				
L1	n.a.	n.a.	4 (33.3%)	n.a.
L2	n.a.	n.a.	1 (8.4%)	n.a.
L3	n.a.	n.a.	7 (58.3%)	n.a.
L4	n.a.	n.a.	0 (0%)	n.a.
CD behavior				
B1	n.a.	n.a.	6 (50%)	n.a.
B2	n.a.	n.a.	3 (25%)	n.a.
B3	n.a.	n.a.	3 (25%)	n.a.
Perianal Disease	3 (12%)	1 (7.6%)	2 (16.7%)	0.94
IBD-related surgery	8 (32%)	4 (30.8%)	4 (33.3%)	0.77
Thiopurines	1 ( 4%)	1 ( 7.6%)	0 ( 0%)	0.96
Biologics	8 (32%)	3 (23.1%)	5 (41.6%)	0.57
Anti-TNF $\alpha$	8 (32%)	3 (23.1%)	5 (41.6%)	0.57
Infliximab	2 ( 8%)	2 (23.1%)	0 (0%)	0.49
Adalimumab	4 (16%)	1 ( 7.7%)	3 (25%)	0.52
Vedolizumab	1 ( 4%)	1 ( 7.7%)	0 (0%)	0.96
Ustekinumab	2 ( 8%)	0 ( 0%)	2 (16.7%)	0.42

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn’s Disease; BMI: Body Mass Index; E1: proctitis; E2: left-sided colitis; E3: pancolitis; L1: ileum; L2: colon; L3: ileum-colon; L4: upper gastrointestinal tract; B1: non stricturing non penetrating; B2: stricturing; B3: penetrating; TNF $\alpha$ : Tumor Necrosis Factor  $\alpha$ .

**Table 3. Characteristics of endometriosis in patients with Ulcerative Colitis and Crohn's Disease.**

	<b>IBD (n=25)</b>	<b>UC (n=13)</b>	<b>CD (n=12)</b>	<b>p</b>
<b>Endometriosis-related symptoms</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
Dysmenorrhea	22 (88%)	13 (100%)	9 (75%)	0.47
Dyschezia	11 (44%)	6 (46.1%)	5 (41.7%)	0.85
Dyspareunia	19 (76%)	10 (76.9%)	9 (75%)	0.72
Dysuria	3 (12%)	3 (23.1%)	0 (0%)	0.24
HMB	16 (64%)	10 (76.9%)	6 (50.0%)	0.32
Infertility	7 (28%)	3 (23.0%)	4 (33.3%)	0.9
<b>Endometriosis Type</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
DIE	25 (100%)	13 (100%)	12 (100%)	n.a
Ovarian endometriosis	12 (48%)	5 (38.0%)	7 (58.0%)	0.43
Adhesions	24 (96%)	12 (92.0%)	10 (83.3%)	0.49
<b>Endometriosis pelvic sites</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
Posterior DIE	21 (84%)	11 (84.6%)	10 (83.3%)	0.64
Retto-sigma	6 (24%)	2 (15.4%)	4 (33.3%)	0.56
RVS	2 (8%)	1 (7.7%)	1 (8.3%)	0.49
Torus	5 (20%)	2 (15.4%)	3 (25%)	0.92
Lateral DIE	16 (64%)	8 (61.0%)	5 (41.6%)	0.43
USL	15 (60%)	11 (84.6%)	4 (33.3%)	<b>0.02</b>
Right USL	3 (12%)	1 (7.7%)	2 (16.6%)	0.94
Left USL	15 (60%)	11 (84.6%)	4 (33.3%)	<b>0.02</b>
Bilateral USL	3 (12%)	1 (7.7%)	2 (16.6%)	0.94
Parametria	1 ( 2%)	0 (0%)	1 (8.3%)	0.96
Endometrioma	12 (48%)	5 (38.0%)	7 (58.0%)	0.43
Right endometrioma	6 (20%)	1 (7.7%)	5 (41.6%)	0.12
Left endometrioma	6 (20%)	4 (30.7%)	2 (16.6%)	0.72
Bilateral endometrioma	0 (0%)	0 (0%)	0 ( 0%)	n.a.
Salpinx	3 (12%)	1 (7.7%)	2 (16.6%)	0.94
Adenomyosis	19 (76%)	11 (84.6%)	8 (66.6%)	0.56
Anterior adenomyosis	9 (36%)	5 (38.5%)	4 (33.3%)	0.88
Posterior adenomyosis	19 (76%)	11 (84.6%)	8 (66.6%)	0.56
Lateral adenomyosis	6 (20%)	4 (30.7%)	2 (16.6%)	0.72

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; BMI: Body Mass Index; DIE: Deep Infiltrating Endometriosis; RSV: Recto-Vaginal Septum; USL: Utero-Sacral Ligament; HMB: Heavy Menstrual Bleeding.