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Alimentary Tract

Dyspareunia and heavy menstrual bleeding as clinical predictors of concomitant endometriosis in Inflammatory Bowel Disease: A multidisciplinary prospective study

Benedetto Neri[a,b,c,1], Mariasofia Fiorillo[a,1], Federica Iacobini[d], Roberto Mancone[a], Raffaele Balice[a], Eleonora Laluci[a], Francesca Fabrizi[d], Michele Lucarelli[a], Consuelo Russo[d], Caterina Exacoustos[d], Livia Biancone[a,*]

[a] Department of Systems Medicine, Gastroenterology Unit, University "Tor Vergata" of Rome, Rome, Italy
[b] Therapeutic GI Endoscopy Unit, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[c] Università Campus Bio-Medico, Rome, Italy
[d] Department of Surgical Science, Obstetrics and Gynecological Unit, University "Tor Vergata" of Rome, Rome, Italy

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ABSTRACT

Background: The association between Inflammatory Bowel Disease (IBD) and endometriosis is undefined.
Aims: The primary aim was to identify clinical predictors of endometriosis in IBD. Secondary aim was to compare symptoms and IBD characteristics in patients with versus without endometriosis.
Methods: Consecutive fertile IBD patients with ≥1 symptom compatible with endometriosis were prospectively enrolled. Pelvic endometriosis was searched by transvaginal ultrasonography (TVUS).
Results: The study population included 82 IBD patients (age: 38 [18-53] years): 41 (50%) Crohn's Disease (CD), 41 (50%) Ulcerative Colitis (UC). Symptoms included: dysmenorrhea (n=72 [87.8%]), dyschezia (n=29 [35.4%]), dyspareunia (n=46 [56.1%]), heavy menstrual bleeding (HMB) (n=50 [60.9%]), chronic abdominal pain (n=22 [26.8%]). TVUS detected endometriosis in 51 (62.2%) patients (CD: 23 [45.1%], UC: 28 [54.9%]), including deep infiltrating endometriosis (DIE) in 44 (86.3%). Dyspareunia, HBM and chronic abdominal pain were more frequent in patients with endometriosis (35 [68.6%] vs 11 [35.5%], p=0.007; 36 [70.6%] vs 14 [45.2], p=0.03; 18 [35.3%] vs 4 [12.9%], p=0.04). Multivariate analysis identifyied dyspareunia and HMB as risk factors for endometriosis (4.7 [1.6-13.9]; p=0.005; 4.3 [1.4-12.9]; p=0.008).
Conclusions: Endometriosis may be highly underestimated in IBD, being mostly represented by DIE. Dyspareunia and HMB should be carefully searched in fertile young IBD patients to roule out an undiagnosed endometriosis.

1. Introduction

Inflammatory Bowel Disease (IBD) and endometriosis are chronic inflammatory disorders sharing several epidemiological, clinical and pathogenetic features. Both diseases occur at young age and are characterized by a chronic relapsing course determining recurrent abdominal pain and change in bowel habits. Diagnosing endometriosis in IBD patients may represent a diagnostic challenge even for experienced clinicians, due to difficulties in distinguishing gastrointestinal symptoms related to IBD, from those related to intestinal localizations of deep infiltrating (DIE) or pelvic endometriosis [1]. Pathogenetic mechanisms, including an inappropriate immune response, have also been suggested to be shared in IBD and endometriosis [2]. Epidemiological evidence support this concept. A large Danish cohort study including over 37,000 women, reported a 50% increased risk of IBD in patients with endometriosis [3].

Recently, a high prevalence of endometriosis in symptomatic IBD patients has been reported [4]. In a prospective case-control study from our group, endometriosis was observed in more than two-thirds of IBD women with compatible symptoms [4]. Moreover, a higher frequency of DIE, posterior adenomyosis, dyspareunia and dyschezia were observed in patients with IBD and concomitant endometriosis when compared to non-IBD controls with endometriosis [4].

* Corresponding author at: Full Professor of Gastroenterology, University "Tor Vergata" of Rome, Via Montpellier, 1, 00133 Rome, Italy.
E-mail address: biancone@med.uniroma2.it (L. Biancone).
[1] Benedetto Neri and Mariasofia Fiorillo contributed equally to this work.

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Whether endometriosis is associated with specific IBD characteristics is also currently undefined. A single case-control study including 51 patients with IBD and endometriosis reported a higher risk of fibrostricturing Crohn's Disease (CD) [5].

The diagnosis of IBD relies on compatible clinical history, signs and symptoms, confirmed by endoscopic, histologic, laboratory and imaging findings [6,7]. Differently, the diagnosis of endometriosis was historically based on laparoscopy with histological confirmation. Non-invasive tools including transvaginal ultrasonography (TVUS) and pelvic magnetic resonance imaging are currently used at this purpose [8,9]. Recently, TVUS has indeed been indicated as a valid diagnostic tool for detecting endometriosis, even without laparoscopic or histological confirmation [10].

Despite the improved knowledge regarding endometriosis, in terms of symptoms, clinical characteristics and diagnostic modalities, the association between IBD and endometriosis remains poorly defined. Available studies at this regard are indeed often retrospective and characterized by a limited sample size.

On the basis of these observations, the primary aim of the present multidisciplinary prospective study was to search for symptoms predictive of endometriosis in patients with IBD. Secondary endpoint was to compare symptoms and clinical characteristics of IBD in patients with versus without endometriosis.

2. Materials and methods

In a prospective study, female fertile IBD patients in regular follow-up at the tertiary IBD center of the University Hospital "Tor Vergata" of Rome (Italy), were enrolled from January 2022 to July 2025.

2.1. Study population

Eligible IBD patients were recruited during scheduled visits, according to the following criteria: 1) well-defined diagnosis of IBD [6,7]; 2) fertile women; 3) age >16 and ≤55 years; 4) regular follow-up (≥2 visits/year); 5) ≥1 among the following symptoms compatible with endometriosis: dysmenorrhea, dyschezia, dyspareunia, dysuria, heavy menstrual bleeding (HMB), and/or chronic abdominal pain; 6) Clinical remission as assessed by the partial Mayo score for Ulcerative Colitis (UC) and the Harvey Bradshaw Index for CD [11,12]; 7) written informed consent to follow the study protocol. Exclusion criteria: 1) missing or incomplete data; 2) menopause; 3) pregnancy; 4) suspected or defined pelvic malignancy.

IBD diagnosis and activity were assessed according to standard criteria [9,10] and classified according to the Montreal classification [13], Mayo score for UC and Harvey-Bradshaw Index for CD [11,12].

2.2. Study protocol

A non-validated questionnaire searching for symptoms compatible with endometriosis was jointly developed by IBD-dedicated gastroenterologists and endometriosis-dedicated gynecologists of the University Hospital "Tor Vergata" of Rome. During scheduled visits for IBD, all compliant patients were requested to fill the questionnaire, and those reporting ≥1 symptom compatible with endometriosis were enrolled. The presence of the following symptoms compatible with endometriosis was considered in the questionnaire: dysmenorrhea, dyspareunia, dyschezia, dysuria, HMB, abdominal and chronic pelvic pain. HMB was patient-assessed, deemed as reliable as when assessed by using the pictorial blood loss analysis chart [14–16]. Symptoms were also re-assessed by endometriosis-dedicated gynecologists during scheduled outpatient visits. During gynecological assessment, the severity of each symptom was graded by using a 10-cm visual analog scale (VAS). Symptoms showing a VAS ≥5 were considered in the analysis.

2.3. Clinical and gynecological assessments

Patients reporting ≥1 symptom compatible with endometriosis in the questionnaire were referred to endometriosis-dedicated gynecologists of the same University Hospital. Each patient was re-screened by dedicated gynecologists for the same symptoms investigated during the IBD-dedicated visit. Abdominal pain was considered chronic when occurring for ≥6 months. Infertility was defined as no pregnancy after 12 months of unprotected intercourses. Any ongoing treatment was recorded. Patients using contraceptives at time of the study were asked to report characteristics of symptoms before treatment. The enrolled IBD patients were studied by using TVUS in order to detect, diagnose and characterize pelvic endometriosis. In the past, various non-invasive methods have been used in order to diagnose endometriosis, including ultrasound, magnetic resonance imaging and computed tomography. However, even recently, the gold standard for diagnosing endometriosis included laparoscopy with histological assessment. According to the recent guidelines of the European Society of Human Reproduction and Embryology (ESHRE), imaging can replace diagnostic laparoscopy, particularly for DIE, ovarian endometriosis and adenomyosis [10]. Moreover, the International Consensus Statement on non-invasive imaging techniques for the diagnosis of pelvic DIE and endometriosis classification systems established that TVUS, performed by a well-trained operator, is the recommended first-line technique, due to its availability, good test performance, cost-effectiveness and non-invasiveness [17].

2.4. Clinical parameters considered

For each patient, the following parameters were prospectively recorded: birth date, Body Mass Index (BMI), IBD duration, IBD type, UC extent [17], CD site and behavior [13], UC and CD clinical activity [11,12] previous and current treatments for IBD (immunosuppressors, biologics, small molecules), smoking status, prior IBD-related surgery. The above-reported symptoms compatible with endometriosis, together with a detailed medical, surgical, obstetric, and gynecological history were also recorded (age at menarche, gravidity, parity, infertility, menstrual cycle characteristics, date of the last menstrual period, previous surgeries).

2.5. Transvaginal ultrasonography

Examinations were performed by the same dedicated gynecologists using Voluson E6, E8, or E10 devices (GE Healthcare; Zipf, Austria) with transvaginal probes (5.0-9.0 MHz). Conventional two-dimensional (2D) TVUS with gray scale and power/color Doppler was carried out. The scan included uterus, adnexa, pouch of Douglas, bladder, ureters, rectum, rectosigmoid junction, anterior/lateral/posterior parametria, rectovaginal septum, vesico-uterine pouch and uterosacral ligaments (USLs) [18]. All endometriosis-related findings (including endometriomas, DIE, adenomyosis) were documented using a standardized ultrasound mapping system, incorporating the International Deep Endometriosis Analysis guidelines [19].

Ovarian endometrioma was diagnosed in case of persistent uni- or multilocular cysts with homogeneous low-level echogenicity and absent or moderate vascularization [18]. DIE was diagnosed according to validated ultrasonographic criteria [17,18–23]: ≥1 lesion in anterior, posterior or lateral compartments with retroperitoneal hypoechoic linear or nodular thickening, irregular contours, and absent or minimal Doppler signals.

Adhesions were suspected when a reduced mobility of the uterus or adnexa was observed during real-time manipulation, associated with endometriosis signs.

Adenomyosis was diagnosed according to the Morphological Uterus Sonographic Assessment consensus [23,24]. The presence of ≥1 direct sonographic feature on 2D or 3D imaging, including myometrial cysts, hyperechoic islands, irregular or interrupted junctional zone was considered at this purpose [21–24]. Endometriosis and adenomyosis were considered separately, although recent evidence suggests symptoms overlap [22].

2.6. Ethical considerations

The study protocol is in agreement with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study was approved by the Independent Ethics Committee of "Tor Vergata" University Hospital of Rome (protocol n. 126/20). All patients provided a written informed consent according to the study protocol.

2.7. Statistical analysis

As the outcome of the study is binary, adequacy of the sample for multivariable modeling was assessed using an events-per-parameter (EPP) framework to limit overfitting and ensure model stability. Using this approach, the effective information for multivariable estimation is determined by the number of outcome events. With an enrolled sample of 118 and an expected 30% dropout/missing outcome rate, the analyzed sample was expected to include approximately 83 participants. On the basis of our previous findings [4], assuming a 60% frequency of endometriosis, the expected number of outcome events was approximately 50 (0.60×83). The resulting EPP for the planned multivariable model would therefore be approximately 7.1 events per parameter (50 events/7 parameters). Accordingly, the present sample size was considered satisfactory for descriptive analyses and for exploratory univariable and multivariable associations.

Data were expressed as median [range] Differences were evaluated using the chi-square test, Fisher's exact test, and the Mann-Whitney test or the Student *t*-test, as appropriate. Predictive factors for endometriosis were investigated by univariate and multivariate logistic regression analysis. Inter-observer agreement was assessed by using the Cohen's kappa coefficient (κ). A p value <0.05 was considered statistically significant.

3. Results

3.1. Study population

During the study period, a total of 118 fertile women with IBD in regular follow-up completed the questionnaire during a scheduled outpatient visit. Among these, 10 patients did not meet the inclusion criteria, while 108 (91.5%) reported ≥1 symptom compatible with endometriosis. Among these 108 patients, 26 (24.1%) patients filled the questionnaire but then declined gynecological assessment. Therefore, the study population included 82 IBD patients who first met the inclusion criteria and then provided the written informed consent for gynecological assessment. Characteristics of the study population are summarized in Supplementary Table 1. As shown, the 82 IBD patients considered in the analysis included 41 (50%) patients with UC and 41 (50%) with CD.

In the group of 41 UC patients, disease extent included proctitis in 13 (31.8%), left-sided colitis in 14 (34.1%) and extensive colitis in 14 (34.1%) patients. Among the 41 CD patients, intestinal lesions involved the ileum in 16 (39%) patients, the colon in 8 (19.5%), and the ileo-colon in 17 (41.5%), with upper GI involvement in 5 (12.2%) patients. CD phenotype was non-fibrostricturing non-perforating phenotype in 22 (53.6%) patients, fibrostricturing in 14 (34.1%) and penetrating in 5 (12.3%) patients.

3.2. Endometriosis in IBD patients

Among the 82 IBD patients reporting in the questionnaire ≥1 symptom compatible with endometriosis, TVUS detected endometriosis in 51 (62.2%) patients (Fig. 1). In the 51 IBD patients with endometriosis, CD and UC patients showed a comparable BMI (21.9 [17.3-29.6] vs. 20.8 [18.8-41.6]; p=0.71) and age at enrollment and at menarche (36 [23–53] vs. 38 [23–53] years, p=0.19; (12 [9–17] vs. 12 [10–17] years, p=0.79, respectively).

3.3. Characteristics of IBD: Comparison between patients with versus without endometriosis

As detailed in Table 1, clinical characteristics of IBD, including IBD type (CD vs UC), UC extent, CD site and behavior, did not significantly differ between patients with versus without endometriosis. Additional clinical features of IBD, including perianal disease, IBD- related surgery and prior major treatments for IBD were also comparable between patients with versus without endometriosis.

3.4. Characteristics of IBD in patients with concomitant endometriosis

When considering the subgroup of 51 IBD patients with concomitant endometriosis detected by gynecologists, there were 23 (45.1%) CD and 28 (54.9%) UC patients (Fig. 1; Table 1). Among the 28 UC patients, the extent included proctitis in 8 (28.6%), left-sided colitis in 11 (39.3%) and pancolitis in 9 (32.1%) patients. Among the 23 CD patients, intestinal lesions involved the ileum in 9 (39.1%), the colon in 4 (17.4%) and the ileum-colon in 10 (43.5%) with upper GI lesions in 4 (17.4%) patients. CD behavior was non-stricturing non-penetrating phenotype in 12 (52.2%) CD patients, fibrostricturing in 9 (39.1%) and penetrating in 2 (8.7%) patients. Among the 23 CD patients, 5 (21.7%) showed perianal disease (Table 1).

3.5. Characteristics of concomitant endometriosis in patients with IBD

Features of endometriosis in patients with IBD are summarized in Table 2. As shown, DIE was diagnosed by TVUS in a high proportion of patients (86.3%). When comparing UC versus CD patients, posterior DIE and right ovarian endometriomas were significantly more frequent in CD patients than in UC patients (14 [60.9%] vs 6 [21.4%]; p=0.009 and 7 [30.4%] vs 1 [3.6%]; p=0.025). Conversely, the involvement of either the USL (left and right) and, separately, the left USL (Fig. 2), were significantly more frequent in the tested UC than CD population (24 [85.71%] vs 11 [47.82%]; p=0.009 and 21 [75%] vs 9 [39.13%]; p=0.02). No other significant differences were found in terms of localization of the endometriotic lesions in UC versus CD patients (Table 2).

3.6. Symptoms compatible with endometriosis

3.6.1. Overall IBD population

When considering all the 82 IBD patients reporting ≥1 symptom compatible with endometriosis, the most frequently reported symptom was dysmenorrhea, recorded in 72 (87.8%) patients, followed by HMB in 50 (60.9%) and dyspareunia in 46 (56.1%). The frequency of the other considered symptoms are reported in Table 3.

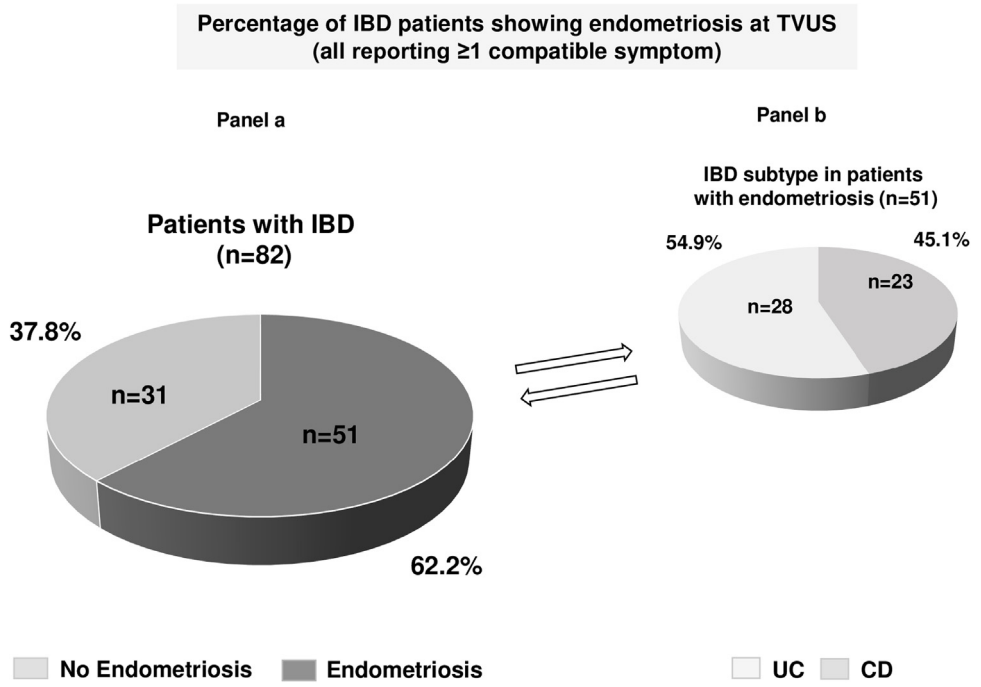

Fig. 1. Panel a: Percentage of patients with endometriosis as detected by transvaginal ultrasonography in the whole group of 82 patients with Inflammatory Bowel Disease (IBD) enrolled. All the 82 patients reported ≥1 symptom compatible with endometriosis in the questionnaire: endometriosis was detected in 62.2% (n=51) of patients. Panel b: IBD subtype (Ulcerative Colitis versus Crohn's Disease) among the 51 patients with endometriosis (45.1% Crohn's Disease; 54.9% Ulcerative Colitis).

Table 1
Clinical characteristics of Inflammatory Bowel Disease patients with Ulcerative Colitis and Crohn's Disease with vs. without concomitant endometriosis.

	UC without endometriosis (n=13)	UC with endometriosis (n=28)	P	CD without endometriosis (n=18)	CD with endometriosis (n=23)	p
Age, median [range]	37.5 [17–48]	35 [23–53]	0.98	35 [24–46]	38 [26–52]	0.06
IBD duration, median [range]	9.5 [1–25]	8 [1–27]	0.97	8 [2–23]	9 [1–35]	0.66
UC extent, n (%)						
E1	5 (38.5%)	8 (28.6%)	0.71	n.a.	n.a.	n.a.
E2	3 (23,0%)	11 (39.3%)	0.48	n.a.	n.a.	n.a.
E3	5 (38.5%)	9 (32.1%)	0.73	n.a.	n.a.	n.a.
CD localization, n (%)						
L1	n.a.	n.a.	n.a.	7 (38.9%)	9 (39.1%)	1
L2	n.a.	n.a.	n.a.	4 (22.2%)	4 (17.4%)	0.71
L3	n.a.	n.a.	n.a.	7 (38.9%)	10 (43.5%)	0.99
L4	n.a.	n.a.	n.a.	1 (5.6%)	4 (17.4%)	0.36
CD behavior, n (%)						
B1	n.a.	n.a.	n.a.	10 (55.5%)	12 (52.2%)	0.99
B2	n.a.	n.a.	n.a.	5 (27.8%)	9 (39.1%)	0.52
B3	n.a.	n.a.	n.a.	3 (16.7%)	2 (8.7%)	0.63
Perianal disease, n (%)	1 (7.7%)	1 (3.6%)	0.53	8 (44.4%)	5 (21.7%)	0.17
IBD-related surgery, n (%)	0 (0%)	3 (10.7%)	n.a.	4 (22.2%)	5 (21.7%)	1
Thiopurines, n (%)	0 (0%)	1 (3.6%)	n.a.	1 (5.6%)	0 (0%)	n.a.
Biologics, n (%)	3 (23%)	4 (14.3%)	0.65	9 (50%)	9 (39.1%)	0.53
Anti-TNFα	3 (23%)	2 (7.1%)	0.3	5 (27.8%)	6 (26.1%)	0.99
Infliximab	0 (0%)	1 (3.6%)	0.99	1 (5.6%)	2 (8.7%)	0.99
Adalimumab	3 (23%)	1 (3.6%)	0.08	4 (22.2%)	3 (13.0%)	0.67
Vedolizumab	0 (0%)	1 (3.6%)	0.99	0 (0%)	0 (0%)	n.a.
Ustekinumab	0 (0%)	1 (3.6%)	0.99	4 (22.2%)	3 (13.0%)	0.67
Upadacitinib, n (%)	0 (0%)	0 (0%)	n.a.	1 (5.6%)	0 (0%)	0.43
Filgotinib, n (%)	0 (0%)	1 (3.6%)	0.99	0 (%)	0 (0%)	n.a.

Abbreviations: IBD=Inflammatory Bowel Disease; UC=Ulcerative Colitis; CD=Crohn's Disease; TNF=Tumor Necrosis Factor; n.a.=not applicable.

3.6.2. IBD patients with concomitant endometriosis

In the subgroup of 51 patients with IBD and concomitant endometriosis, the most frequently reported symptoms included dysmenorrhea (46 [90.2%]), HMB (36 [70.6%]) and dyspareunia (35 [68.6%]). The frequency of the other compatible symptoms are reported in Table 3.

3.6.3. Symptoms in IBD patients with versus without endometriosis

Table 3 summarizes the frequency of symptoms reported in the questionnaire by IBD patients with or without endometriosis. As shown, dyspareunia, HMB and abdominal pain were significantly more frequently reported by IBD patients with versus without endometriosis (35 [68.6%] vs 11 [35.5%], p=0.007; 36 [70.6%] vs

Table 2
Characteristics of endometriosis in patients with Inflammatory Bowel Disease, Ulcerative Colitis and Crohn's Disease.

	IBD with endometriosis (n=51)	UC with endometriosis (n=28)	CD with endometriosis (n=23)	p*
DIE, n (%)	44 (86.3%)	24 (85.7%)	20 (86.9%)	0.77
Anterior DIE, n (%)	0 (0%)	0 (0%)	0 (0%)	n.a.
Posterior DIE, n (%)	20 (39.2%)	6 (21.4%)	14 (60.9%)	**0.009**
Rectum-sigmoid colon, n (%)	9 (17.6%)	3 (10.7%)	6 (26.1%)	0.28
RVS, n (%)	2 (3.9%)	1 (3.6%)	1 (4.3%)	0.56
Torus, n (%)	9 (17.6%)	2 (7.1%)	7 (30.4%)	0.07
Vagina, n (%)	0 (0%)	0 (0%)	0 (0%)	n.a.
Lateral DIE (USL), n (%)	36 (70.6%)	24 (85.7%)	12 (52.2%)	**0.02**
USL, n (%)	35 (68.6%)	24 (85.7%)	11 (47.8%)	**0.009**
Right USL, n (%)	7 (13.7%)	3 (10.7%)	4 (17.4%)	0.77
Left USL, n (%)	30 (58.8%)	21 (75%)	9 (39.1%)	**0.02**
Bilateral USL, n (%)	3 (5.9%)	0 (0%)	3 (13.1%)	0.08
Parametrium, n (%)	1 (1.9%)	0 (0%)	1 (4.3%)	0.45
Endometrioma, n (%)	14 (27.5%)	6 (21.4%)	8 (34.8%)	0.45
Right endometrioma, n (%)	8 (15.7%)	1 (3.6 %)	7 (30.4%)	**0.02**
Left endometrioma, n (%)	7 (13.7%)	5 (17.8%)	2 (8.7%)	0.59
Bilateral endometrioma, n (%)	1 (1.9%)	0 (0%)	1 (4.3%)	0.45
Tuba, n (%)	4 (7.8%)	0 (0%)	4 (17.4%)	**0.03**
Right tuba, n (%)	3 (5.9%)	0 (0%)	3 (13.1%)	0.08
Left tuba, n (%)	3 (5.9%)	0 (0%)	3 (13.1%)	0.08
Bilateral tuba, n (%)	2 (3.9%)	0 (0%)	2 (8.7%)	0.19
Adenomyosis, n (%)	32 (62.7%)	16 (57.1%)	16 (69.6%)	0.53

* Comparison between Ulcerative Colitis and Crohn's Disease.
Abbreviations: IBD=Inflammatory Bowel Disease; UC=Ulcerative Colitis; CD=Crohn's Disease; TNF=Tumor Necrosis Factor; USL=Utero-Sacral Ligament; DIE=Deep Invasive Endometriosis; RVS=Recto-vaginal septum; n.a.=not applicable.

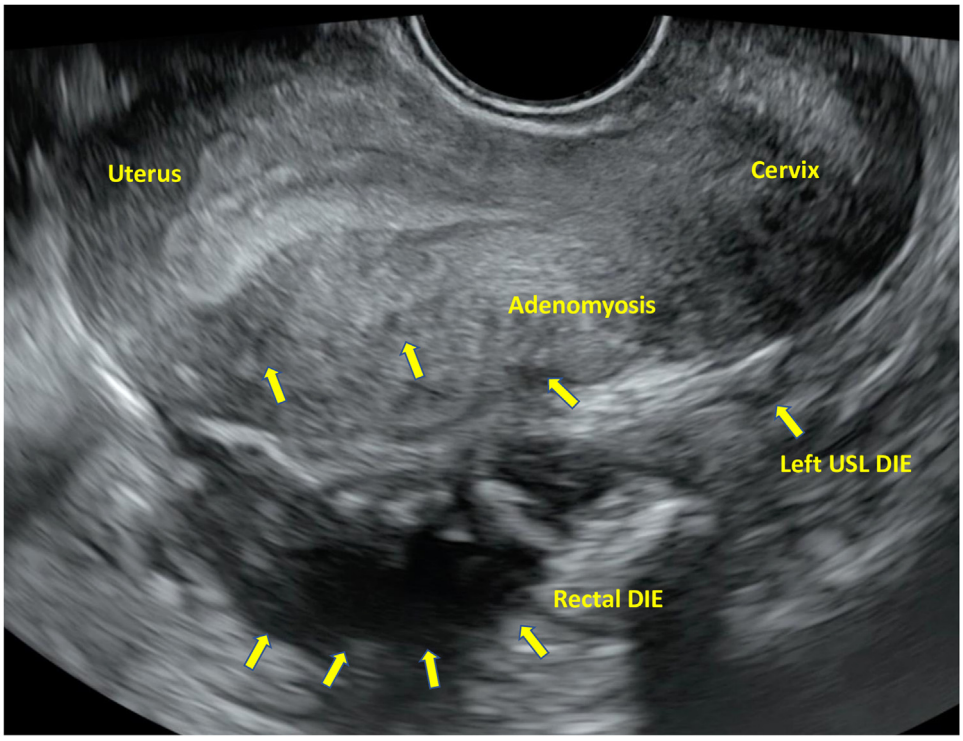

Fig. 2. Transvaginal ultrasonographic appearance of adenomyosis associated with deep infiltrating endometriosis in one patient with Crohn's Disease. Gray-scale longitudinal section showing the uterus with adenomyosis with hyperechoic islands (yellow arrows in the uterus). Posterior to the uterus, a hypoechoic endometriotic fibrotic nodule infiltrating the muscular layer of the anterior rectal wall and the left utero-sacral ligament is detected (yellow arrows).

14 [45.2%], p=0.03; 18 [35.3%] vs 4 [12.9%]; p=0.04, respectively) (Fig. 3).

The frequency of these symptoms was also comparable between UC and CD patients with endometriosis (Supplementary Table 2).

3.7. Predictive factors for concomitant endometriosis as assessed by gastroenterologists

In the tested IBD population, univariate and multivariate analyses were used in order to identify symptoms predictive of en-

Table 3
Demographic and clinical characteristics related to endometriosis in Inflammatory Bowel Disease patients with versus without endometriosis.

	IBD (n=82)	IBD with endometriosis (n=51)	IBD without endometriosis (n=31)	p
Age, median [range]	38[17-53]	37 [23–53]	36 [17–48]	0.44
BMI, median [range]	21.9 [17.3-41.6]	21.6 [17.3-41.6]	21.2 [17.6-29.4]	0.99
Menarche age, median [range]	12 [9–17]	12 [9–17]	12 [9–16]	0.91
Dysmenorrhea, n (%)	72 (87.8%)	46 (90.2%)	26 (83.9%)	0.61
Dyschezia, n (%)	29 (35.4%)	15 (29.4%)	14 (45.2%)	0.22
Dyspareunia, n (%)	46 (56.1%)	35 (68.6%)	11 (35.5%)	**0.007**
Dysuria, n (%)	9 (10.9%)	7 (13.7%)	2 (6.5%)	0.51
Heavy Menstrual Bleeding, n (%)	50 (60.9%)	36 (70. 6%)	14 (45.2%)	**0.03**
Infertility, n (%)	10 (12.2%)	9 (17.6%)	1 (3.2%)	0.11
Chronic pelvic pain, n (%)	24 (29.3%)	18 (35.3%)	6 (19.4%)	0.19
Abdominal pain, n (%)	22 (26.8%)	18 (35.3%)	4 (12.9%)	**0.04**

Abbreviations: IBD=Inflammatory Bowel Disease; BMI=Body Mass Index.

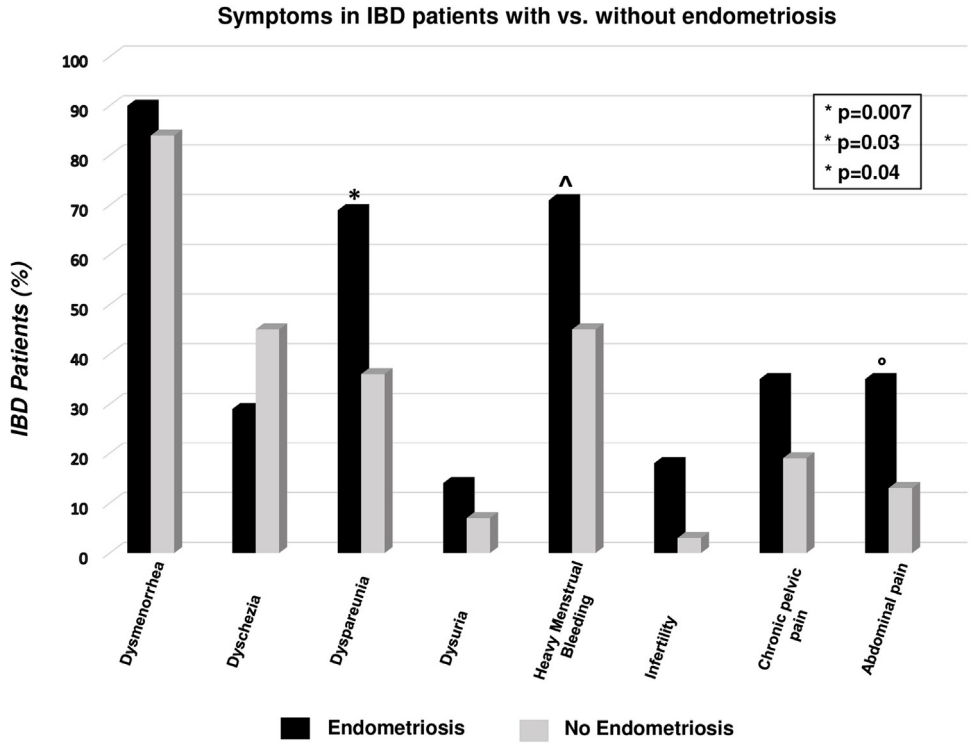

Fig. 3. Histograms detaling the frequency of each symptom compatibile with endometriosis when compating patients with Inflammatory Bowel Disease (IBD) with versus without endometriosis detected by transvaginal ultrasonography. As shown, the frequency of dyspareunia, heavy menstrual bleeding and abdominal pain was significantly higher in IBD patients with vs. without a subsequent diagnosis of endometriosis (p=0.007, p=0.03 and p=0.04, respectively).

dometriosis. As shown in Supplementary Table 3, univariate analysis identified as significant predictive factors for endometriosis dyspareunia (OR 3.9 [1.5-10.2]; p=0.004), HMB (OR 2.9 [1.1-7.4]; p=0.02) and abdominal pain (OR 3.7 [1.1-12.2]; p=0.03).

In the tested IBD population, multivariate analysis confirmed that independent predictive factors for endometriosis were dyspareunia (OR 4.7 [1.6-13.9]; p=0.005) and HMB (OR 4.3 [1.4-12.9]; p=0.008). Conversely, multivariate analysis did not confirm abdominal pain as a risk factor for endometriosis in IBD (OR 2.8 [0.76-10.6], p=0.12) (Supplementary Table 3).

3.8. Interobserver agreement between gynecologists and gastroenterologists

The inter-observer agreement between gastroenterologists and gynecologists in terms of assessment of symptoms compatible with endometriosis showed substantial concordance in detecting dyspareunia (κ=0.77) and dyschezia (κ=0.67). Differently, moderate agreement was observed for dysmenorrhea (κ=0.40), dysuria (κ=0.42), and HMB (κ=0.50) (p<0.001 for all).

4. Discussion

Recent findings suggest that in fertile women with IBD, a concomitant diagnosis of endometriosis may be underestimated even by experienced gastroenterologists [4,25,26]. Several factors may play a role in this finding, including potential overlapping symptoms occurring in patients with IBD and endometriosis [26–28]. Additional potential confounders may be that scheduled IBD visits are mainly focused on gastrointestinal symptoms and that limited awareness exists among non-specialists regarding endometriosis-related symptoms. Recent evidences emphasize the need to consider a diagnosis of endometriosis in IBD patients with demographic and clinical features compatible with this gynecological disease [3,4].

On the basis of these observations, this issue was further addressed in the present study. Our findings support that a high frequency of endometriosis may be detected in IBD patients with compatible symptoms searched by dedicated gastroenterlogists and gynecologists. In the tested population, endometriosis was detected by TVUS in more than 60% of symptomatic fertile IBD patients. It seems worthwhile to consider that the reported high frequency of endometriosis in our study population was observed in the subgroup of IBD patients reporting in the questionnaire ≥1 symptom compatible with endometriosis. In particular, among symptoms considered, dyspareunia, HMB and chronic abdominal pain were more frequently reported by IBD patients with versus without endometriosis. Accordingly, multivariate analysis identified dyspareunia and HMB as symptoms predictive of a subsequent diagnosis of endometriosis. This result may assume relevance in clinical practice, as the above reported symptoms may be underestimated or erroneously attributed to IBD, thus leading to a delayed/missed diagnosis and potentially to inadequate treatments. Present findings are consistent with those reported in a previous study from our group, showing a surprisingly high prevalence of endometriosis in symptomatic IBD patients, particulatly of DIE [4].

In our study population, more than two/thirds of IBD patients with concomitant endometriosis indeed showed DIE, at a higher frequency than in the general non-IBD population [29]. This observation suggests that women with IBD may represent a subgroup at risk for DIE requiring expert gynecological and TVUS assessment for a proper diagnosis. The high frequency of DIE observed in our cohort further supports that diagnosing endometriosis in IBD patients requires not only the systematic search for specific symptoms, but also dedicated gynecological assessments in referral centers. The diagnosis of DIE is indeed known to be more challenging than that of ovarian endometriomas, highlighting the need of endometriosis-dedicated specialists [4,10]. Therefore, the identification of a non-invasive and reliable diagnostic technique for endometriosis in IBD patients represents a clinically relevant issue, potentially preventing unnecessary treatments. In our study, TVUS was confirmed as a highly effective diagnostic technique, according to current dedicated guidelines [10]. Moreover, findings from the present study support the relevance of a multidisciplinary approach in order to optimize clinical management of these patients, as already reported in other clinical situations [30].

In our study cohort, endometriosis involving the USL was significantly more frequent in patients with UC than with CD. In these patients, symptoms as tenesmus and chronic pelvic pain may be related to the location of the endometriotic nodules, potentially involving the sigmoid colon and rectum. In the tested IBD population, the site of IBD lesions and CD phenotype appeared not to influence the frequency and type of endometriosis. This finding may suggest that endometriosis should be searched in IBD patients with symptpms compatible with this condition, irrespectively of the type of IBD (CD vs UC), localization of IBD lesions and of CD phenotype.

In order to identify IBD patients at higher risk of endometriosis, a simple non-validated questionnaire was developed in agreement with the referral gynecologists. The questionnaire included the most frequently symptoms associated with endometriosis. A good inter-observer agreement between dedicated gastroenterologists and gynecologists was observed in terms of symptoms assessment. Although the questionnarire used in our study is not validated, it was employed to avoid a potential selection bias when recruiting IBD patients during scheduled visits. The reported findings suggest its usefulness for identifying IBD patients with endometriosis. Present observations may provide new data leading to the development of a currently missing validated questionnaire for this purpose. Irritable Bowel Syndrome (IBS)-like symptoms are common also in IBD, affecting up to 25% of patients, even during deep remission [31]. Searching for specific symptoms, including those reported in the questionnaire, may help IBD-dedicated gastroenterologists to search for endometriosis.

Among the main limitations of the present study there is the lack of a control population including patients with endometriosis without IBD and the limited sample size. Nevertheless, at the best of our knowledge, current evidence at this regard includes very few prospective studies regarding IBD and endometriosis [4]. This is particularly true when considering the search for endometriosis in IBD. Moreover, the present study included prospectively enrolled IBD patients without a diagnosis of endometriosis despite compatible symptoms. This last group allowed comparisons in terms of clinical characteristics of IBD between patients with versus without endometiosis. All the tested IBD patients from both groups referred in the questionnaire at least one symptom compatible with endometriosis, subsequently detected in more than half (62%) of patients. In the tested population, clinical characteristics of IBD appeared not to influence the frequency of endometriosis but this finding needs to be confirmed in larger studies. Adenomyosis may determine symptoms comparable to endometriosis, particularly HMB [22]. In order to avoid potential confounders, only predictors for a concomitant diagnosis of endometriosis, not including isolated adenomyosis, were considered in the present study.

Among the strengths of the study, there is the homogeneous cohort of IBD patients followed-up at a referral center, with demographic and clinical characteristics classified according to current European guidelines [25]. This feature of the tested population should avoid bias related to an inappropriate diagnosis and assessments of IBD. Supporting this concept, clinical characteristics of the tested cohort were comparable to those observed in the general IBD population, thus suggesting the reliability of our findings. Additional strengths include the prospective study design and the assessment of all IBD patients in the same referral IBD and endometriosis-dedicated gynecological Units. Due to difficulties related to a proper diagnosis and characterization of endometriosis, this multidisciplinary approach should optimize a proper diagnosis of this condition in IBD.

In conclusion, a high prevalence of endometriosis, frequently characterized by deep localization, may be detected in fertile IBD patients referring at least one compatible symptom. Among compatible symptoms, dyspareunia and HMB have been identified as predictive of a diagnosis of endometriosis in IBD patients. These symptoms should therefore be carefully searched by gastroenterologists when assessing fertile IBD patients, in order to promptly refer patients to dedicated gynecologists. Considering the potential relevance of present findings deriving from a relatively small sample size, adequately powered studies are needed to confirm these results in larger IBD populations.

A multidisciplinary approach involving experienced gastroenterologists and gynecologists, may improve the diagnostic rate of endometriosis, thus allowing a timely and proper treatment of this concomitant condition in patients with IBD. Early diagnosis and personalized therapeutic strategies may improve the quality of life of young IBD women with underestimated symptoms related to endometriosis.

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Author's contribution

Conception and design of the study **(LB, BN)**, acquisition of data **(MF, RM, FI, FF, ML, EL, RB, CR)**, analysis and interpretation of data

(MF, BN), drafting the article or revising it critically for important intellectual content **(LB, MF, BN, CR, CE)**, final approval of the version to be submitted **(LB)**.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the paper entitled "Dyspareunia and heavy menstrual bleeding as clinical predictors of concomitant Endometriosis in Inflammatory Bowel Disease: a multidisciplinary prospective study".

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Supplementary materials

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