REVIEW

DOI: http://dx.doi.org/10.15403/jgld-6456

Intestinal Endometriosis, A Challenge for Gastroenterologists: A Narrative Review

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Received: 14.04.2025
Accepted: 06.08.2025

ABSTRACT

Endometriosis is a medical condition where endometrial tissue and glands are found outside the uterine cavity: on ovaries, pelvic peritoneum, rectovaginal septum, bladder, bowel and more. The ectopic tissue is estrogen dependent and cause inflammation and immune response and is responsible for chronic pain, infertility and disability of these patients. Without a specific biomarker and with a wide range of symptoms, the diagnosis is often overlooked or delayed. Abdominal and pelvic pain together with dysmenorrhea, dyspareunia, irregular bleeding, and cyclic alteration of intestinal habits are a challenging combination of symptoms that characterise endometriosis. One of the less recognized yet significant causes of abdominal pain is intestinal endometriosis. Gastroenterologists and gynecologists must solve the intricate puzzle of gynecological, gastrointestinal and nonspecific symptoms that are present in patients with intestinal endometriosis; further managements should be decided by a multidisciplinary team. This review aims to present the pathogenic mechanisms, diagnostic challenges and treatment while highlighting the importance of recognizing intestinal endometriosis as a potential differential diagnosis in patients with gastrointestinal symptoms.

Key words: endometriosis – intestinal endometriosis – IBS – IBD – abdominal pain.

Abbreviations: CGRP: calcitonin gene-related peptide; COC: combined oral contraceptives; DIE: deep infiltrating endometriosis; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; MRI: magnetic resonance imaging; OE: ovarian endometrioma; TRUS: transrectal ultrasound; TVUS: transvaginal ultrasound.

INTRODUCTION

Abdominal pain is a common complaint with a broad differential diagnosis in women. There is a long list of diseases that may cause abdominal pain, from benign conditions such as irritable bowel syndrome (IBS) to life threatening malignancies (Table I) [1]. Intestinal endometriosis is one of the less recognized but still significant causes for abdominal pain and the patients are often misdiagnosed or suffer a significant delay in correct diagnosis or excessive surgery. This form of endometriosis, where ectopic endometrial tissue is present within the intestines mimics several gastrointestinal and gynecological disorders and makes the accurate diagnosis more challenging and crucial [2].

DEFINITION

Endometriosis is a painful chronic gynecological inflammatory disease, estrogen-dependent, characterized by the presence of endometrial tissue (endometrial glands and stroma) outside of the uterus. It is a challenging condition with regard to its diagnosis and therapy [4].

EPIDEMIOLOGY

The prevalence of endometriosis is generally evaluated to 7-10% of the feminine population [5] but with significant variations (from 2 to 18%) [6]; estimates vary depending on the specific study design, information source, and case definition. Eskenazi and Warner [7] in 1997 found a 6-10% prevalence, Saria-Santamera et al. [8] in 2020 1-5%, while the Endometriosis Guideline Development Group (ESHRE) 2022 acknowledges 2-10% [4].

Table I. Main conditions that cause abdominal pain in women [3]

CONDITION	TYPICAL SYMPTOMS	KEY DIAGNOSTIC FEATURE
IBS	Abdominal pain, constipation or/ alternating with diarrhea, bloating	Rome IV criteria, exclusion diagnosis
Inflammatory bowel disease (IBD)	Abdominal cramping, chronic diarrhea, weight loss	Ulceration ore strictures of intestine on endoscopy
Endometriosis	Chronic or cyclic pelvic pain, diarrhea, bloating, dyschezia, dysmenorrhea	Lesions identified with laparoscopy, MRI showing "chocolate cysts", ultrasound
Appendicitis	Right lower quadrant pain, nausea, vomiting	CT scan shows inflamed appendix
Diverticulitis	Left lower quadrant pain, fever, constipation alternating with diarrhea	CT scan shows diverticular inflammation
Pelvic inflammatory disease	Pelvic tenderness, fever, purulent discharge	Clinical criteria, positive cultures from cervix
Acute pancreatitis/ chronic pancreatitis	Severe epigastric pain that radiate to the back, usually worsened after meals of alcohol consumption Nausea, vomiting	Amylase and lipase elevated in serum CT scan shows pancreatic inflammation or calcifications
Cholelithiasis Cholecystitis	Right upper quadrant pain Radiates to the right Fever, jaundice	Murphy's signs positive Ultrasound shows gallbladder wall inflammation or /and gallstones Altered liver tests
Urinary tract infection Urolithiasis	Low abdominal pain or pelvic pain Dysuria, frequent urination, urgency to urinate small amount	Urine analysis: leukocyte, blood, nitrites Ultrasound: stones at different levels of urinary tract
Psoas abscess Retroperitoneal hematoma	Back or flank pain, poorly localized Fever, shock symptoms	CT scan or MRI shows fluid collection or accesses in retroperitoneal space
Abdominal wall hernia	Pain localized at hernia site Palpation of a bulge emerging from the abdominal wall	Physical examination CT scan or ultrasound

A 2021 meta-analysis provided new data on its prevalence: an overall of 18% prevalence, with variations depending on the stage of the disease from 2% to 20% [6]. This interval is obtained due to the high heterogeneity of studies included in this meta-analysis. Also, there are differences of prevalence between patient's categories by the principal symptoms of infertility, chronic pelvic pain or asymptomatic [6].

From adolescence to perimenopause, no age is spared of the possibility of having endometriosis. The disease can show first symptoms shortly after the first menses that can persist for e long time, until after menopause, intermittent or continuously.

The dominant symptom of endometriosis is chronic pelvic pain and is strongly associated with infertility. The other symptoms are complex and may mimic pathology associated with other systems: gastrointestinal, urinary, nervous system [9]. 35-50% of the women diagnosed with infertility and chronic pelvic pain were proven to have endometriosis [10].

Because of these, endometriosis has gained a place at the top of list of diseases that affect considerably the quality of life of patients [11].

LOCALISATION

In terms of localization, the endometriotic lesions are mostly encountered in the pelvis but can exist also in the abdomen, lungs, urinary system, skin, diaphragm, and inguinal region [12, 13]. Genital endometriosis is the presence of endometriotic implants in the pelvic cavity, on reproductive organs. The main sites for endometriosis are the ovaries, uterus and posterior peritoneum [14]. The most typical localization of extragenital endometriosis is the intestine [15] which is affected in 5-12% of the women diagnosed with endometriosis [16].

Sigmoid colon and rectum are involved in almost 90% of these cases [16]; from these patients, sigmoid and rectum layers are affected in almost 74% and the rest of cases are localized in the recto-vaginal septum [17]. Ileum endometriosis is less frequent (1-7%) [18] and rarer locations are represented by the appendix (2.8%) and cecum [19]. There are three types of endometrioses: deep infiltrating endometriosis (DIE)-lesions that infiltrate deeper than 5 mm, ovarian endometrioma (OE), and superficial endometriosis [11, 16]. Colon endometriosis can appear as superficial disease lining the serosa or as deeply infiltrative lesions of the muscularis or mucosa [15].

PATHOGENESIS

Theories regarding the development of intestinal endometriosis have been proposed since the early 20th century and continue nowadays to offer complex but only partial explanations to this disease. The first one is named "Retrograde menstruation theory" or Sampson's theory and remains the cornerstone in understanding endometriosis. Basically, it states that menstrual blood containing endometrial tissue, refluxes through the fallopian tubes into the peritoneal cavity, where the cells contained in it implant in the structures around and also on the surface of intestine [20]. Another theory proposes that endometrial cells travel via lymphatic and blood vessels and implant in distant sites [21]. Surgical implantation

implies that during caesarean sections and other gynecological surgeries a transplant of endometrium into peritoneal cavity inadvertently happens. This mechanism is particularly relevant given the raising numbers of caesarean sections globally [22, 23]. Moving forward, coelomic metaplasia offers another explanation to the development of intestinal endometriosis through the transformation of peritoneal mesothelial cells intro endometrial-like cells under the influence of hormones [24]. A familial predisposition has been observed, suggesting genetic and epigenetic influence in intestinal endometriosis' pathogenesis [25, 26].

A recent study has highlighted the role of calcitonin gene-related peptide (CGRP), a neuromodulator that shapes immunity in neuroimmune interactions and pain communication in endometriosis. CGRP is a key mediator in migraine and also involved in inducing inflammation and promoting endometriosis, present in both human and mouse endometriosis lesions [27].

DIAGNOSIS

One of the pillars of diagnosis is detailed history and symptom correlation, identifying cyclic patterns of symptoms or gastrointestinal symptoms that worsen during menses.

The suspicion of intestinal endometriosis rises after a detailed anamnesis and a careful review of clinical signs. Vaginal examination can offer the first clues of existence of endometriotic nodules [28].

Clinical Diagnosis

The symptoms are cyclical and related with estrogen-dependent inflammation that occurs to the endometrial tissue localized outside of uterine cavity but not all the patients are symptomatic, only 2/3 of them have symptoms [5, 29].

Chronic pelvic pain is the dominant symptom and exists at 60% of the women diagnosed with endometriosis and infertility is the next major concern of those patients [30, 31].

Endometriosis most common symptoms belong to gynecological pathology but also mimic intestinal diseases. Gynecological complaints are dysmenorrhea, pelvic pain, dyspareunia, heavy and irregular bleeding during periods or between [29].

It is very common that patients with endometriosis to exhibit gastrointestinal symptoms as bloating and alternation of constipation with diarrhea, rectal bleeding, nausea, vomiting [15, 31].

From one study we learn that the symptoms of DIE varied depending on the organ involved, and that DIE involving the colon was linked to more frequent noncyclical and general gastrointestinal pain and pain when sitting [32].

Intestinal endometriosis is correlated with cyclical pain, with bowel specific symptoms such as constipation, diarrhea, dyschezia and rectal bleeding, and some non-specific manifestation such as dysmenorrhea, dyspareunia. It is proven that not all the patients with intestinal endometriosis are symptomatic, with no correlation between the intensity of symptoms and the size of the lesions [33].

In terms of location-related symptoms, sigmoid and rectal endometriosis was more commonly associated with cyclic defecation pain, cyclic constipation, profound dyspareunia, diarrhea, hematochezia and longer stool evacuation times than other regions [14, 34].

Differential diagnosis of intestinal endometriosis includes primary gastrointestinal conditions such as IBS, inflammatory bowel disease (IBD), diverticulitis and colorectal cancer but also gynecological conditions such as ovarian cysts, pelvic inflammatory disease and adenomyosis [5, 35].

There is a notable overlap of intestinal endometriosis symptoms with IBD and particularly IBS, as they both exhibit pain, bloating, altered bowel habits, the main characteristics of IBS (Table II) [11, 35]. In this situation can be even more challenging to diagnose correctly because the symptoms of endometriosis may exhibit a cyclic nature and are often exacerbated during menstruation, resembling the symptom patterns observed in IBS [36]. This is a functional gastro-intestinal disorder that affects 4% of the population, according to the Rome Foundation Global Study [37], and is moderately higher in women than in men. It is defined by abdominal pain and alteration of frequency and form of the stool. There are no specific biomarkers for IBS, the diagnosis is based on symptoms

Table II. Main differences in common symptoms in IBS vs. endometriosis patients

	IBS	Endometriosis
Pain	Moderate abdominal pain, upper abdominal symptoms	Abdominal pain is more severe, lower abdominal pain more often
Upper GI symptoms	Early satiation, GERD, eating associated nausea	Nausea associated with menstruation
Menstrual related symptoms	In menstrual fare-up, bowel habits change, pain isn't worsening	In menstrual flare-up, pain is worsening
Rectal symptoms	Rectal bleeding with red blood, possibly from hemorrhoids or tears	Rectal bleeding with dark color blood, painful defecation is frequent
Progressiveness	Symptoms tend to stability, not progress	Severe pain with bowel movements, Symptoms have tendency to worsen in time
Diet effect	Diet may bring positive effects on symptoms	
Specifics		Dyspareunia, vaginal, rectal and general pelvic pain History of infertility, multiple miscarriages and ectopic pregnancies

(Rome IV criteria) and its symptoms also can flare up during menstruation. Also, as in endometriosis, it affects considerably the quality of life of the patients [38].

It was shown that 50% of women with persistent pelvic pain exhibit symptoms suggestive of IBS, but also 37% of women with IBS have endometriosis, compared with 15% that have endometriosis without being diagnosed with IBS [39, 40]. Irritable bowel symptoms symptoms can flare up during menstruation in about 20% of the cases and numerous women who have bowel endometriosis are misdiagnosed with having IBS [31].

In terms of the severity of the symptoms, one study found that women with mild or minimal endometriosis have more severe IBS symptoms than women with severe to moderate endometriosis [41].

One meta-nalysis of the existent data on the correlation between endometriosis and IBS confirmed that the frequency of IBS is higher in patients already diagnosed with endometriosis, compared to controls (women without endometriosis) but this does not indicate clearly some causality. There is a two to three-fold higher probability that a patient with endometriosis would also be diagnosed with IBS [11, 29].

Women with endometriosis had higher rates of hospitalization, abdominal surgery, and total healthcare use than women without the condition, according to a new study that examined gastrointestinal symptoms and healthcare resource utilization in women with and without the condition [42].

Imaging Techniques for Diagnosis

Imaging methods used for diagnosis are transvaginal ultrasound (TVUS) which offers a 95-98% sensitivity for retrocervical illness and 98-100% for rectosigmoid localization and transrectal ultrasound (TRUS) that has a 88-96% sensitivity for localization below rectosigmoid junction [16, 43].

Magnetic resonance imaging (MRI) offers a more complete view of the abdomen and pelvis and if the patient has special bowel preparation or bladder contrast before the investigation, the visualization of the lesions is more accurate [44].

Rectosigmoidoscopy and colonoscopy offer information and help to make differential diagnosis, identifying strictures, perforations and other lesions that can be secondary to deep infiltrative endometriosis or belong to other diseases as IBD or malignancy [45].

Diagnostic Laparoscopy

Although the upper techniques combined can corroborate a good view of the lesions localization and extension, the ultimate tool for a definitive diagnosis and also treatment is laparoscopy- the "golden standard", as multiple sources from literature name it. The histopathological confirmation of the biopsy successfully completes the diagnostic process along with laparoscopy [46].

Diagnostic Biomarkers

It was a constant challenge for clinicians to find reliable diagnostic markers for endometriosis, but until now no marker appears to fill the blanks. A systematic review of blood biomarkers evaluated 47 of 122 blood biomarkers and only four were evaluated in a sufficient number of studies: CA-125, CA19.9, interleukin-6 and anti-endometrial antibodies Among them, the most studied biomarker was CA-125, with different cut-off points in different studies and was the only one present in sufficient studies, but it does not qualify as a was a diagnostic or triage test. The value of CA-125 > 43 U/ml was an efficient diagnostic test in one study. Still, CA-125 and

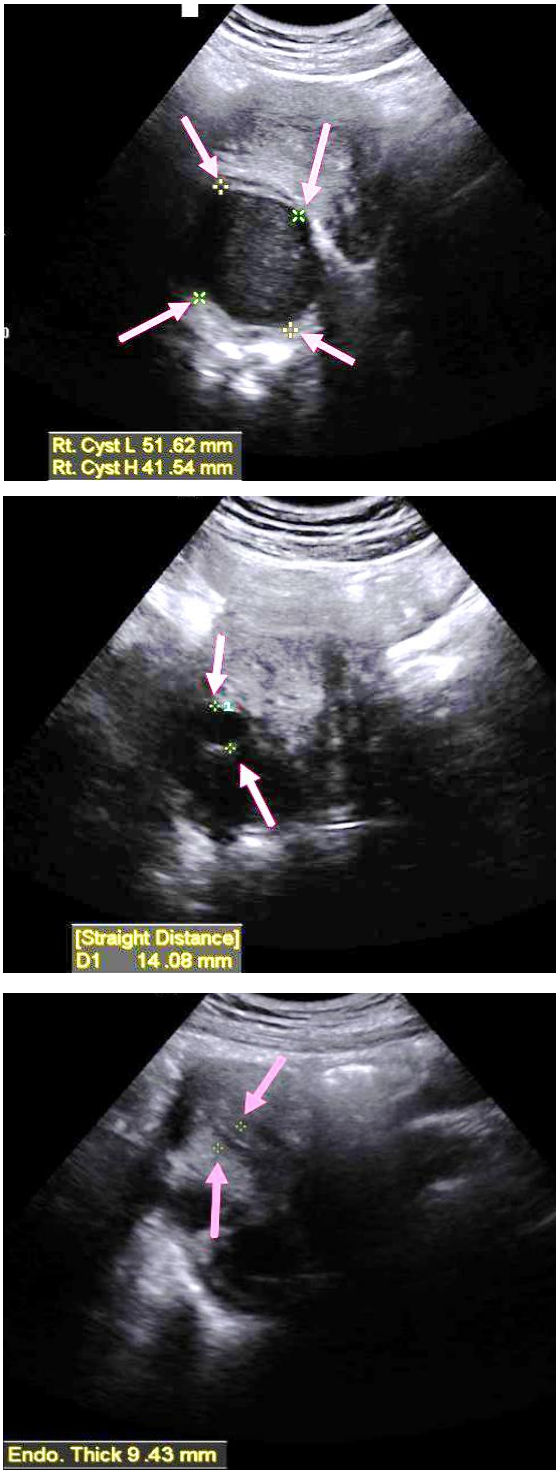

Fig.1A, B, C. Transabdominal ultrasound of the same patient following the 3-year evolution (A-2022,B- 2023, C-2024) of an endometrial cyst localized in rectouterine space and resolution after pregnancy.

continues to be used as diagnostic orientation because has a significant correlation with endometriosis [47]. It is best used in postoperative monitoring of the patients, as its levels decrease after surgery and rise again if endometriosis recurs [44, 48].

Two recent studies have used saliva and serum-based microRNA panel for diagnosing endometriosis with high sensitivity (96.7%) and specificity (100%). Their results suggest that microRNA biomarkers may be the much-needed non-invasive tool for the diagnosis of endometriosis [49, 50].

Diagnostic Errors

Common diagnostic pitfalls of intestinal diagnosis are symptom overlap, imaging limitations and delayed suspicion of endometriosis. Intestinal endometriosis often presents itself with gastrointestinal and nonspecific symptoms such as: abdominal pain, bloating, diarrhea, often cyclically present, leading to misdiagnosis as IBS or IBD. Small or deep, infiltrative lesions of endometriosis, may escape to standard imaging modalities as ultrasound or computed tomography scan. Clinicians may not include endometriosis in differential diagnosis from the outset, mostly in women that do not have a history of typical pelvic symptoms [15, 51, 52].

A summary of diagnostic and treatment approaches is summarized in Fig 2.

TREATMENT

Treatment of endometriosis has two main objectives: pain control and resolving infertility. The fertility issue may be secondary to some patients but pain management crucial in obtaining a good quality of life that lacks in those women.

Pain encountered in endometriosis has its origin in inflammation and visceral hypersensitivity. Some pelvic pain syndromes are associated with endometriosis: IBS, bladder pain syndrome, vulvodynia and abdomino-pelvic myalgia. The mechanisms with a role in their genesis are central, peripheral and cross-sensitization [16, 46].

Treatment options for endometriosis include medical and surgical options. Before discussing treatment, patients should be investigated for complications like intestinal lumen stenosis and sub occlusive symptoms, for presence of tumors or any annexal masses larger than 5 cm and if any ureter or renal abnormalities are found [53].

A stepped approach model Is recommended, where medical options come first and if the treatment does not deliver the expected results or the patient does not tolerate the medication then the therapy should switch to surgical intervention [54].

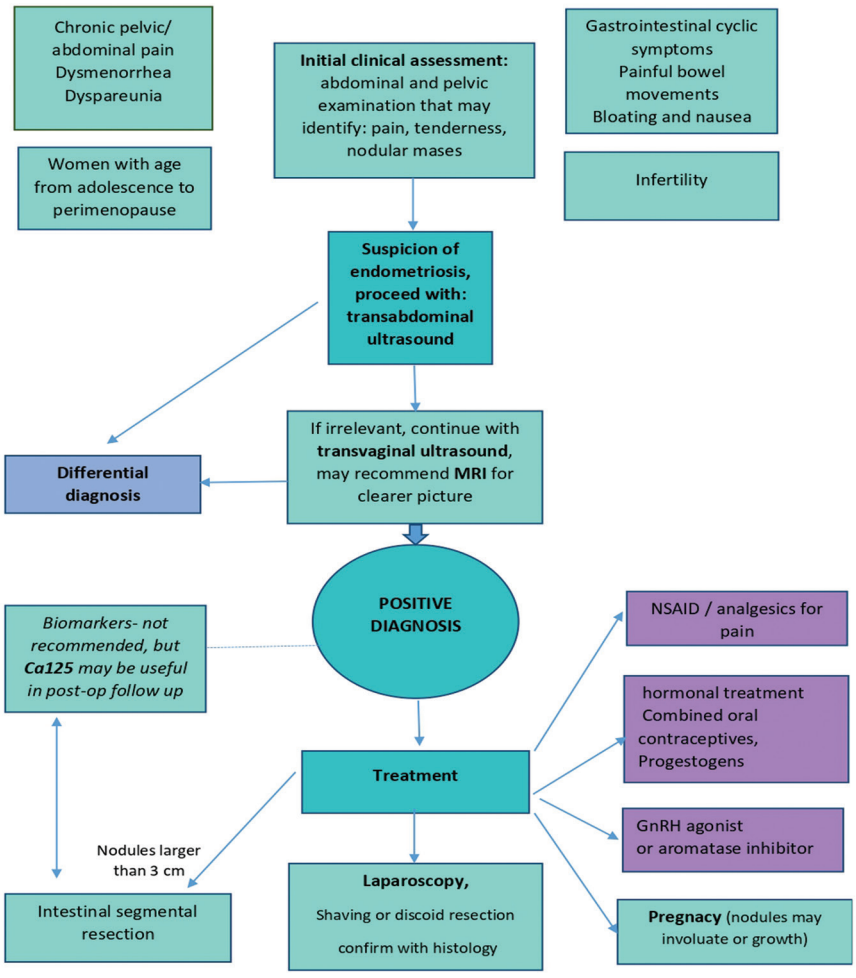

Fig. 2. Flowchart for diagnostic and treatment of endometriosis

Non-surgical Treatment

Medical therapy efficiency in cases of intestinal endometriosis is not backed by optimal data. It consists of hormonal medication. Combined contraceptives are the first line of medication, appropriate for mild symptom cases. They can be in the form of combined oral contraceptives (COC), transdermal patch and vaginal ring [53, 55]. Hormonal treatment acts on ectopic endometrium with a suppressing effect and obtains a decrease of inflammation, which is one of the main pathways of the symptoms in endometriosis [56, 57]. COC appear to be more efficient in continuous than cyclical regimen administration in controlling dysmenorrhea, non-menstrual pain and dyspareunia [58].

Progestogens are another option for hormonal treatment, which can be administered orally, intramuscular, intrauterine dispositive or subcutaneous [59]. Some of the recommended progestogens are: medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, and noretisterone acetate. They are effective in controlling dyspareunia caused by deep infiltrative endometrioma and pain associated with endometriosis [44].

Another category of hormonal medications are GnRh agonists that suppress the secretion of endogenous gonadotrophins. Studies show improvement in pains scores of dysmenorrhea in patients treated with GnRH [60]. GnRH agonists cause a pseudo menopausal state by activating GnRH receptors, which desensitize the body and inhibit gonadotropin output [16]. There is promising but limited evidence for the efficacy of GnRH antagonists on endometriosis associated pain. Elagolix, an GnRh antagonist, can be used to treat moderate to severe pain in endometriosis but studies have shown that it causes a dose-dependent decrease in bone density which should be completed with hormonal replacement. Aromatase inhibitors are reserved to refractory pain, which cannot be controlled with other medications or surgery [61, 62].

Women with intestinal endometriosis whom main concern is fertility should be carefully advised regarding the secondary effects and complications of the hormonal medication [63].

Blocking the receptor CGRP/ RAMP1 with CGRP inhibitors that are used to treat or prevent migraine has reduced the pain and lesion size in mice. This may be a promising future treatment for many patients that are suffering bbecause of the ineffectiveness of available treatments at prezent [27].

Lifestyle Treatment Option

As in any other condition that has unclear physiopathology and complex symptoms, endometriosis patients may find some relief from symptoms by making some lifestyle choices. Most important changes refer directly to diet. Taking into consideration the proposed mechanisms for endometriosis, those dietary approaches are at least theoretically justified, but are not supported by solid or congruent studies results. It was observed that a low FODMAP diet that is recommended to IBS patients has some beneficial results in endometriosis patients [40].

Also it is speculated that a gluten free diet may be effective given the symptom overlap that this condition has with celiac disease. The adherence on these diets for a long period of time may have substantial adverse effects on fiber intake that is associated with disturbances of intestinal microbiota, permeability dysfunction of the intestinal wall, low production of anti-inflammatory substances such as short chain fatty acids (SCFA) [64, 65].

The patients that are willing to implement changes in diet, must consider no further than the general recommendation of the World Health Organisation (WHO): restriction of red meat, salt and refined carbohydrates and polyunsaturated fatty acids and reasonable intake of foods rich in mono/polyunsaturated fatty acids, fruits, vegetables and whole grains [66].

A so-called anti-inflammatory diet with no spices, animal fats, caffeine alcohol and reduced dairy products along with phytoestrogens from specific sources are among the recommendations that can alleviate the symptoms of endometriosis [67].

Surgery

Different locations of endometriosis dictate the recommendation: rectovaginal and rectosigmoid junction endometriosis has had good response to medical therapy, with good results in pain management, while endometriosis of the proximal sigmoid colon has a recommendation of surgical excision because of a moderate risk for obstruction. Some of the surgical techniques that are used to treat intestinal endometriosis depending on the localization and extent of lesions are lesion shaving, nodulectomy and segmental resection [56].

Surgical excision of endometrial implants using minimal invasive techniques such as laparoscopy is the most effective and stands as a golden standard in treatment of endometriosis. Excision of nodules larger than 3 cm, drainage of cysts, removing adhesions, are a few of the techniques used in these types of intervention [68].

Persistent pain can be treated by excision of the endometrial implants by laparoscopy and this makes this intervention a valuable tool not only for diagnosis but also for treatment [60].

In literature we can find proof that patients with refractory and intense pain can benefit from a hysterectomy with oophorectomy with a rate of almost 90% of pain relief. Recurrent pain in those patients was reported in 10% of the cases. Hormonal substitution with combined hormonal medication should not be forgotten in these patients. The use of estrogen only increases the risk of microscopic disease [69].

Intestinal endometriosis exposes the patient to a risk for occlusive or sub-occlusive syndrome (estimates to less than 1%) e due to stenosis, rectovaginal fistula, adhesions, rectal bleeding. In those cases, segmental intestinal resection is necessary [70]. Case reports have shown that there is a particular risk for intestinal obstruction in patients that use hormonal treatment because some of the endometriotic nodules may grow in volume during suppressive hormonal therapy [71].

CONCLUSIONS

Intestinal endometriosis should be suspected in a patient of premenopausal age, with chronic symptoms such as pain, bloating, constipation, or diarrhea, maybe blood in stool and pain at intercourse, that become more severe cyclically - related

to menses. This review aims to spotlight the importance of investigation for gynecological morbidities in patients presenting with gastrointestinal complains.

Accurate diagnosis requires a thorough medical history and several diagnostic techniques, including high-accuracy ultrasound (transvaginal or transrectal), MRI with bowel preparation and laparoscopy.

It may be difficult to distinguish between intestinal endometriosis and IBS but an early diagnosis can improve significantly the quality of life of the patients that often wander among physicians for years before getting the right diagnosis. Treatment of intestinal endometriosis consists of surgery or a combination of medical and surgical treatments. Surgical intervention is superior to the use of medications when comparing relief of pain symptoms and fertility outcomes. A multidisciplinary approach is the key to successfully treating those patients.

Conflicts of interest: None to declare.

Authors' contribution: A.N.G. conceived the manuscript, drafted the initial version of the article. R.G. conducted literature review and provided high-quality ultrasound images. D.L.D. proposed the research theme, guided the project and revised the manuscript. All authors have read and approved the final version of the manuscript.

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