Chronic pelvic pain (CPP) is a debilitating, lifelong struggle for some individuals. The diagnosis and treatment of CPP also contribute to significant annual healthcare costs in the United States (US). The most common diagnoses associated with CPP include endometriosis, interstitial cystitis, irritable bowel syndrome (IBS), myofascial pain, pelvic floor hypertonia, and dysmenorrhea. In reality, CPP in women often represents undiagnosed endometriosis that may contribute to these other associated pain syndromes. Since a diagnosis of endometriosis requires surgery, there is a delay in the diagnosis of endometriosis of greater than 11 years in the US.

For some practitioners, symptoms including bowel, bladder, and pelvic complaints are recognized manifestations of endometriosis. For other healthcare providers, the diagnosis of endometriosis is rarely considered. A lack of appreciation for the morbidity associated with endometriosis may be the primary reason for our failure to diagnose the majority of patients who present with CPP.

Irritable bowel syndrome is a common functional gastrointestinal disorder associated with diarrhea (IBS-D), constipation (IBS-C), or both (IBS-M). IBS is diagnosed on the basis of a characteristic cluster of symptoms—recurring bouts of abdominal discomfort or pain relieved by defecation and associated with a change in the frequency and/or consistency of stools—in the absence of structural or biochemical abnormalities. Diagnostic criteria are often loosely applied in the clinical setting, and the underlying cause is never defined in many individuals. Diet and changes in the bowel microbiome have been implicated in the etiology of IBS. Bile acid malabsorption has also been documented in up to a third of individuals with IBS-D.

IBS patients incur higher annual healthcare costs compared to those without IBS, with spending ranging from $1562 to $7547 per year for the average IBS patient. Annually, IBS is estimated to result in $1.6 billion in direct costs and $19.2 billion in indirect costs in the US alone.

It can be argued that IBS is a constellation of symptoms that includes bloating, diarrhea, constipation, and varied other bowel complaints, rather than a defined disease. In general, gastroenterologists (GIs) and others specializing in gastroenterology complaints are largely unaware of the strong links between IBS and endometriosis; therefore, it is rarely included in the differential diagnosis for bowel complaints. This fact may contribute to the poor satisfaction of patients with current IBS treatments. In a recent survey, IBS caused daily symptoms in 43% of patients; under 20% were satisfied with treatments they had received. A better understanding of the pathophysiology of this disorder would likely lead to more effective treatments and earlier resolution of symptoms.

The pathophysiology of IBS includes immune activation, increased gut permeability, and visceral hypersensitivity. Endometriosis is also a highly inflammatory and immune-regulated disorder, raising the possibility that IBS could well be a response to local or systemic inflammatory changes associated with this disease. C-reactive protein (CRP) has been used to differentiate IBS from irritable bowel disease (IBD). CRP has also been shown to be systemically elevated in women with endometriosis. Autoimmune dysfunction is common in endometriosis, but autoimmunity has been reported in patients with IBS as well.

In population studies, the majority of patients with IBS are women. Female sex is the single
greatest risk factor for development of IBS. Over 50% of women report cycle-dependent worsening of IBS during menses. All of these associations suggest that endometriosis may be a major contributor to IBS in women. In this review, we will address these questions and provide a case series in support of this hypothesis.

Effect of Female Sex and Hormones on IBS

Menstrual Cycles and IBS

IBS has been noted to be highly related to female sex and to age, but not to race. There is a 2:1 ratio of women to men with IBS, and symptoms of IBS are frequently related to the menstrual cycle. Women with IBS report significantly more abdominal pain, bloating, intestinal gas, constipation, and diarrhea at the time of menses compared to controls. Whitehead and colleagues found that 50% of female IBS patients compared to 34% of non-IBS patients reported worsening bowel symptoms during menses. Heitkemper and colleagues reported prospective data confirming that IBS patients report worse stomach pain, nausea, and diarrhea during menses compared to healthy controls. The worsening of IBS symptoms with menses is analogous to symptoms reported by women with endometriosis, who report increasing dysmenorrhea at the time of menses.

The link between endometriosis and IBS is strengthened further by the observation that dysmenorrhea itself is associated with IBS. Treatment with GnRH agonist therapy to suppress endometriosis and cause cessation of menses improves symptoms in both IBS and endometriosis sufferers. Symptoms of IBS are improved after menopause, similar to what is reported for endometriosis.

Menstrual Cycle Effects on Pain

The menstrual cycle affects pain sensitivity, with distinct differences in somatic compared to visceral pain. In the rat model, which has a 4-day estrus cycle, heightened somatic sensitivity to skin stimulation occurs during proestrus and estrus phases (high estrogen), while visceral pain sensitivity was higher during metestrus and diestrus phases, comparable to perimenstrual or menstrual phase in women. The relationship between pain sensitivity and phase of the menstrual cycle, while variable in women, follows a similar pattern with somatic pain sensitivity greatest in mid-cycle and visceral pain sensitivity greatest at menses, at least in IBS patients.

Dysmenorrhea results in large part to prostaglandin release, and women with IBS are more likely to experience dysmenorrhea than women without IBS. In women with IBS, estrogen and progesterone may have an impact on visceral pain thresholds, and prostaglandins released during menstruation might influence those thresholds.

The menstrual cycle has been shown to have an impact on bowel function in other ways. Gastroenterology transit time is prolonged in the luteal phase of the menstrual cycle and reduced when estrogen and progesterone levels fall right before menses. Stools tend to become loose during menses in women with IBS, suggesting faster gastrointestinal transit may be related to this symptom.

Bharadwaj and colleagues suggested that prostaglandins, which are higher during menses, contribute to IBS symptoms including abdominal pain, bloating, and diarrhea. Crowell and colleagues reported that women with dysmenorrhea have greater menstrual-related variation in pain sensitivity. The higher levels of prostaglandins in menstrual fluid is associated with a greater risk of having endometriosis. The inflammation associated with endometriosis promotes cyclooxygenase-2 expression and prostaglandin production. IBS symptoms at menses may, therefore, be exaggerated specifically in the setting of endometriosis, raising the question of whether IBS is merely gastrointestinal reaction to having endometriosis. This association also raises the question of whether endometriotic implants on or near the bowel is required for the symptoms of menstrual-related IBS.

Menopause

The influence of sex hormones on IBS is supported by data from women in menopause. Prevalence of IBS in women decreases markedly after menopause. In a survey of 5430 households in the US, frequency of IBS decreased after age 45 in women while remaining unchanged in men. Similar trends have been reported in the United Kingdom (UK) and Germany that document an age-related decrease in IBS in women after age 50–65, although symptoms may worsen in the perimenopause before improving later after menopause.

Mathias and colleagues have demonstrated that artificial menopause induced with GnRH agonist leuprolide decreased IBS symptoms. Conversely, a cohort study in the UK reported an increase in IBS symptoms in hormone replacement therapy (HRT) users compared to non-users. Fillingim and Edwards showed a decrease
in somatic pain thresholds (increased pain sensitivity) in postmenopausal women receiving hormone therapy.59

Pregnancy
Sex hormone levels are high during late pregnancy. Early survey data from the University of North Carolina found that a majority of women with IBS reported a reduction in symptoms during pregnancy,60 which may reflect lack of hormone fluctuations and absence of menses during the 9 months of pregnancy. Pregnant women have a higher likelihood of being constipated, perhaps because of the smooth muscle relaxation effect of progesterone or the compression of the bowel by the growing fetus.

Endometriosis
Endometriosis is an estrogen-dependent, inflammatory condition affecting women from menarche to menopause.31 It is present in 5%–10% of the general population but in up to 70% of women with pelvic pain. Endometriosis is characterized by a constellation of symptoms including painful periods (dysmenorrhea), painful intercourse (dyspareunia), and painful bowel movements (dyschezia). In addition, subtle signs of endometriosis have been recognized, and are related to a hormonal disturbance known as progesterone resistance, leading to infertility, spotting before menses, and luteal phase defect. Systemic manifestations of the inflammatory milieu associated with endometriosis are also thought to contribute to more global symptoms including malaise, chronic fatigue, and IBS.22

Endometriosis is defined as the presence of ectopic endometrium, composed of glandular and/or stromal elements outside of the uterine cavity. This material gets deposited inside the pelvis at the time of menstruation, likely from retrograde menstruation.61 Genetic predisposition plays a dominant role in its pathogenesis.62,63

We, and others, have documented that the presence of this ectopic tissue in the pelvis and elsewhere can generate a significant systemic inflammatory response.16,64-66 Inflammatory changes have been shown to improve after treatment, but as a relapsing disease, a return of inflammation can occur as menstruation resumes.

Association Between Endometriosis and IBS
Bowel and bladder complaints are common in women with endometriosis.67 Up to a third of women with endometriosis report gastrointestinal changes at the time of menses—over 50% of women with IBS note cycle-specific worsening of symptoms.68 Compared to controls, women with endometriosis are 3.5 times more likely to have an IBS diagnosis.69 Implants of endometriosis on the bowel have been reported in 3.8%–37% of women diagnosed with endometriosis.70

Essentially all studies exploring the association between endometriosis and IBS have focused on women first diagnosed with endometriosis. Wu et al studied 6076 subjects with endometriosis and found that 15% had IBS.71 Hansen compared endometriosis patients to controls and reported that 22% had symptoms of IBS.67 Surprisingly, no studies to date have examined women with IBS and asked how many have endometriosis. While up to a third of endometriosis patients have bowel implants, it remains unknown how many women with IBS have endometriosis and how many of those have lesions on or near the bowel.

Most women with IBS are under- or misdiagnosed.72 Nasim et al points out that bowel endometriosis is often not considered or included in the differential diagnosis for acute or chronic abdominal complaints.73 In our practice, we perform laparoscopy routinely for CPP and have examined a subset of women with complaints specific to IBS. This study is the first to examine women with IBS and perform laparoscopy for determination of endometriosis.

As shown in Table 1, the finding of endometriosis was uniformly positive in these women. In 12 consecutive laparoscopies in women identified with IBS, 12/12 (100%; 95% CI: 75% to 100%) were found to have endometriosis present. The 95% confidence interval (CI) reflects an important finding, worthy to pursue further investigation. Perhaps more important, the stage of disease was generally minimal or mild disease; in all but 1 case, endometriosis was found on or near the rectum, in the pouch of Douglas (posterior cul-de-sac).

Although these data are preliminary, they suggest that endometriosis is a predominant finding in women with menstrual cycle-related IBS and may reflect direct irritation of endometriosis on nearby bowel. As women with IBS have other symptoms of endometriosis (eg, dysmenorrhea), it would be important to better define this population in future studies.

This finding of posterior cul-de-sac disease in the majority of IBS patients suggests that local inflammation secondary to the endometriotic implant may directly contribute to symptoms of IBS. Only
Table 1
Findings at laparoscopy and at pathology for women with symptoms of IBS.

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age</th>
<th>Parity</th>
<th>Operative Findings</th>
<th>Pathology</th>
<th>Stage</th>
<th>On Bowel?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>G0</td>
<td>Endometriosis everywhere but especially on rectum. Implants on anterior and posterior cul-du-sac. Normal uterus and bilateral tubes/ovaries.</td>
<td>Confirmed, endometriosis; proliferative endometrium</td>
<td>3</td>
<td>yes</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>G0</td>
<td>Posterior pelvic sidewalls, none in cul-de-sac. There were multiple obvious endometriosis implants along the left pelvic side wall.</td>
<td>Confirmed, endometriosis; secretory phase endometrium</td>
<td>2</td>
<td>no</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>G0</td>
<td>Adjacent to rectum on right. Normal appearing bilateral fallopian tubes with small endometriosis implant on right mesosalpinx.</td>
<td>Confirmed, endometriosis</td>
<td>2</td>
<td>yes</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>G0</td>
<td>Endometriosis adjacent to rectum on left. Uterus: enlarged, multinodular. Fibroids: 3.5 cm fundal near left cornual region; 5 cm right anterior subserosal. Left ovary: several surface implants of endometriosis with 8 mm endometrioma.</td>
<td>Confirmed, endometriosis; secretory phase endometrium</td>
<td>2</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>G3P3003</td>
<td>Endometriosis on rectum. Absent right tube and ovary. Multiple areas of white stellite scarring consistent with endometriosis on midline posterior cul-de-sac</td>
<td>Confirmed, endometriosis; proliferative phase endometrium</td>
<td>1</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>G0</td>
<td>Posterior cul-de-sac and left side wall endometriosis. Abnormal with peritoneal window and thickened peritoneum. Left ovary: abnormal adherent to omentum and bowel on left.</td>
<td>Confirmed, endometriosis; inactive endometrium</td>
<td>1</td>
<td>yes</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>G1P1</td>
<td>Endometriosis seen on posterior cul-de-sac on rectum. Normal uterus; surgically absent left tube and ovary.</td>
<td>Confirmed, endometriosis</td>
<td>1</td>
<td>yes</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>G0</td>
<td>Posterior cul-de-sac disease. Anterior cul-de-sac: abnormal with endometriosis across the bladder. Midline posterior cul-de-sac: abnormal with endometriosis to the right of the rectum and above, near the termination of the uterosacral ligament. Left pelvic sidewall below the area of the ureter. Left ovary: endometriosis.</td>
<td>Confirmed, endometriosis; benign proliferative phase endometrium</td>
<td>2-3</td>
<td>yes</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>G0</td>
<td>Endometriosis on rectum, multiple endometriotic implants identified and resected including left and right ovarian lesions, a lesion under the ovary on the left, and implants across the left uterosacral.</td>
<td>Confirmed, endometriosis</td>
<td>2</td>
<td>yes</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>G0</td>
<td>Endometriosis on rectum; endometrioma on left ovary, endometriosis throughout left pelvic sidewall, posterior cul-de-sac, right pelvic sidewall, bilateral uterosacral ligaments, bilateral ovaries, posterior uterine serosa, and small endometriosis implant on anterior cul-de-sac.</td>
<td>Confirmed, endometriosis; early secretory phase endometrium</td>
<td>3</td>
<td>yes</td>
</tr>
<tr>
<td>11</td>
<td>23</td>
<td>G0</td>
<td>Endometriosis with large nodule on rectum; left ovary stuck to sidewall. Endometriosis on bladder, left sidewall, cul-de-sac, right side wall, out of the pelvis on the right abdominal wall, and on the right ovary. Endometriosis on appendix, which was twisted on itself because of endometriosis.</td>
<td>Confirmed, endometriosis; proliferative phase endometrium</td>
<td>4</td>
<td>yes</td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>G2P2002</td>
<td>Nodules on small intestine and colon. Endometriosis of the right pelvic sidewall, right ovary, left pelvis, anterior abdominal wall left side, 2 areas on the large intestine (sigmoid colon), 1 area on the small intestine at the area of the cecum (terminal ileum).</td>
<td>Confirmed, endometriosis</td>
<td>3</td>
<td>yes</td>
</tr>
</tbody>
</table>
A true association between endometriosis and IBS would be supported by reduced symptoms after treating endometriosis. Both surgical and medical treatments for endometriosis have been described. Drossman identified 13 women with IBS who had endometriosis treated surgically by resection. They reported that 83% of participants experienced complete relief of symptoms following surgery.

Medical therapy has also been reported to improve IBS symptoms. Ferrero treated 6 patients with colorectal endometriosis with 6 months of norethindrone acetate (2.5 mg/d) and the aromatase inhibitor Letrozole (2.5 mg/d) and reported improvement in 67% of subjects (4/6). Neither study included controls, and the number of treated subjects was low. Prospective studies are needed to further study the effect of treating IBS in women with endometriosis.

Summary and Conclusions

Recognizing the association between endometriosis and IBS represents a great challenge for clinicians treating women. Endometriosis is rarely included in the differential diagnosis for gastrointestinal complaints, even though evidence now strongly suggests it may be a primary cause of both IBS and a similar syndrome, interstitial cystitis. Most female IBS patients are never diagnosed with endometriosis, even though a cause-and-effect relationship exists. Both medical and surgical treatments for endometriosis reduce IBS symptoms, and cessation of menses either medically or after menopause decreases symptoms in both conditions.

Mechanisms of IBS may reflect local inflammation caused by endometriosis on or near the bowel in affected individuals. This finding is supported by our case study in which 11 of 12 subjects had posterior, rectal endometriotic implants present. GIs and clinicians treating gastrointestinal complaints should consider endometriosis as a likely diagnosis in reproductive-aged women with IBS, especially when symptoms worsen at menses.

Future studies are planned to prospectively and rigorously define IBS and to determine the prevalence of endometriosis in this group of women. Further, it will be important to study whether surgical resection or medical treatment of endometriosis will lessen or eradicate the symptoms of this common condition, given that effective and long-term cures for IBS remain limited.
Abbreviations and Acronyms

CPP = chronic pelvic pain; US = United States; IBS = irritable bowel syndrome; IBS-D = irritable bowel syndrome with diarrhea; GIs = gastroenterologists; CRP = C-reactive protein; UK = United Kingdom; HRT = hormone replacement therapy; CI = confidence interval; DIE = deep infiltrating endometriosis

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References


59. Fillingim RB, Edwards RR. The association of hormone replacement therapy with experimental