

Patients With Chronic Pelvic Pain: Endometriosis or Interstitial Cystitis/Painful Bladder Syndrome?

Charles W. Butrick, MD

ABSTRACT

Background: Endometriosis and interstitial cystitis/painful bladder syndrome share similar symptoms. Interstitial cystitis was once considered rare, but it is now recognized as more common than previously thought. This review examines evidence that patients presenting with symptoms typically attributed to endometriosis or with unresolved pelvic pain after treatment for endometriosis may, in fact, have interstitial cystitis, and suggests approaches for appropriate diagnosis.

Methods: A MedLine search using “chronic pelvic pain,” “endometriosis,” “interstitial cystitis,” and “bladder origin pain” as key words was performed for the most recent English-language articles. Additional references were obtained through cross-referencing the bibliography cited in each publication.

Discussion: The symptoms of endometriosis and interstitial cystitis frequently overlap, and these 2 conditions may even coexist in the same patient. In cases of unresolved endometriosis and persistent pelvic pain, patients may have interstitial cystitis. A variety of tools are available to aid in identifying interstitial cystitis.

Conclusion: Gynecologists should be alert to the possible presence of interstitial cystitis in patients who present with chronic pelvic pain typical of endometriosis.

Key Words: Chronic pelvic pain, Endometriosis, Interstitial cystitis, Bladder origin pain.

INTRODUCTION

Endometriosis and interstitial cystitis (IC) are common causes of chronic pelvic pain (CPP) in women.^{1–6} Chronic pelvic pain is commonly defined as noncyclic pain lasting for 6 months or longer and whose severity leads to medical care or functional disability. Chronic pelvic pain accounts for approximately 10% of referrals to gynecology practices, 12% of hysterectomies, and more than 40% of gynecologic diagnostic laparoscopies.^{1,7–11} However, determining the origins of CPP is often challenging because many conditions can cause pelvic pain. A complicating factor is that patients with CPP often have more than one disorder that might cause pain.^{1,7,12,13} To optimize patient outcomes, it is important to identify and treat all potential causes of CPP.

Endometriosis, a common cause of CPP, is diagnosed in up to 80% of patients with CPP.^{2–5} However, increasing evidence suggests that IC is more prevalent than was previously thought and may play a significant role in the cause of CPP.⁶ The importance of considering the urinary bladder as a source of pain was emphasized in a study at a regional center specializing in CPP that investigated the prevalence of IC in patients who experienced persistent or recurrent pelvic pain after undergoing a hysterectomy for CPP. Of the 111 patients enrolled, 88 (79%) were diagnosed with bladder dysfunction consistent with IC.¹⁴ This diagnosis was based on positive findings from one or both cystoscopy and a potassium sensitivity test (PST), a procedure that may identify patients with abnormal bladder epithelial permeability.¹⁵ A positive PST finding has been demonstrated in approximately 80% of patients with IC.^{15,16} The results of this study indicate that IC should be considered in all patients who present with CPP, even those previously diagnosed with other conditions such as endometriosis. Patients with unresolved or refractory CPP should be given an evaluation for IC as well, preferably before any invasive surgical procedure.

Other clinical studies also have indicated that many women who present with CPP may have IC, and that IC and endometriosis are often concurrent conditions in the same patient.^{17–20} A multicenter study by Parsons et al¹⁷ in 3 US gynecology practices found that among 134 patients presenting with pelvic pain, 114 (85%) had a positive PST,

The Urogynecology Center, Overland Park, Kansas and Kansas University Medical Center, Kansas City, Kansas, USA.

Dr Butrick has received grant/research support from Astellas Pharma and Urogen and serves on the advisory board and speakers' bureau of Ortho-McNeil Pharmaceutical. Article supported by Ortho Women's Health & Urology, a division of Ortho-McNeil Pharmaceutical, Inc.

Address reprint requests to: Charles Butrick, MD, The Urogynecology Center, 12200 West 106th St, Ste 130, Overland Park, KS 66215, USA. Telephone: 913 307 0044; Fax: 913 227 0094; E-mail: CButrick@aol.com.

© 2007 by JSL, *Journal of the Society of Laparoendoscopic Surgeons*. Published by the Society of Laparoendoscopic Surgeons, Inc.

which suggests that their pain may have had a bladder component. These results provide further support for gynecologists to give greater weight to IC than in the past in the differential diagnosis of pelvic pain.¹⁷ Early identification of IC in patients with CPP may also result in better treatment outcomes.

OVERVIEW OF ENDOMETRIOSIS

Symptoms commonly associated with endometriosis include perimenstrual lower abdominal pain and dyspareunia.² However, patients with endometriosis can also present with dysuria, hematuria, urinary frequency, and painful voiding, particularly if the bladder is involved.^{2,21} Patients with endometriosis may have no symptoms at all, and the pain typically ascribed to endometriosis often has little correlation with the location or extent of the disease.^{2,22} Therefore, the clinician should consider other causes of pain, even if endometriosis is diagnosed.

Endometriosis is defined as the presence and growth of endometrial mucosa, glands, and stroma outside of the uterus.² Common sites of implantation include the ovaries, uterosacral ligaments, cul-de-sac, and the uterovesical peritoneum.^{21,22} As with the normal uterine endometrium, these extrauterine implants remain under the cyclic influence of ovarian hormones, and are stimulated to grow and then break down with each menstrual cycle.²² Pain is caused by inflammation that results from cyclic sloughing of these endometrial glands, by the release of neurokinins, and by pressure and traction on surrounding tissue from adhesions, if they are present.

Endometriosis is suspected based on the patient's history and physical examination, and confirmed by histologic findings from laparoscopic-guided biopsy. It is essential to ask about symptoms like dyspareunia and urinary urgency/frequency. During the physical examination, the physician may detect tender nodules and masses in the pelvic region, a tender retroverted uterus, or implants in uterosacral ligaments. Visualization of lesions by laparoscopy, with confirmation by biopsy, is considered the "gold standard" for diagnosis.² Evidence increasingly suggests that biopsy is required to confirm the diagnosis of endometriosis.²² In a study by Walter et al²³ that investigated the accuracy of laparoscopic visualization alone in making a diagnosis, only 49% (67/138) of sites that appeared visually positive for endometriosis had positive histology on biopsy. Findings responsible for the false-positives included endosalpingiosis, malignancies, carbon deposits from previous ablations, and other abnormalities, as well as normal peritoneum.²³

Optimal approaches to the management of endometriosis are determined by many factors, including either or both the patient's desire for fertility augmentation and pain relief, the patient's age, and the stage of disease. The approach can be pharmacologic, surgical, or a combination of both. Analgesic therapy with nonsteroidal antiinflammatory agents is appropriate for the patient with mild, premenstrual endometriosis-related pain.^{22,24} The goals of hormone therapy are to interrupt the growth of endometrial tissue implants by suppressing estrogen production or to promote the atrophy of such implants through progestational agents, or both of these. Combined estrogen-progestin oral contraceptives (OCs) are generally considered first-line hormone therapy. Low-dose, continuous, monophasic OC regimens (versus intermittent OC regimens) appear to be effective for suppressing endometrial growth. Other therapies that may be used include progestational agents like medroxyprogesterone acetate and norethindrone acetate, the weak androgen danazol, and gonadotropin-releasing (GnRH) agonists like leuprolide, nafarelin, or goserelin.^{22,24} It is important to note that suppressive hormone therapies, such as GnRH agonists and OCs, also may have beneficial effects for patients with IC, irritable bowel syndrome, and almost any pain disorder that is associated with perimenstrual symptom flares.^{25,26} Therefore, pain relief on suppressive hormone therapy does not necessarily equate with a diagnosis of endometriosis, or even the presence of a gynecologic disorder.

Pharmacologic therapy often succeeds in suppressing pain symptoms and halting the progression of endometriosis. However, once treatment is discontinued, endometriosis will commonly become active again. For women with moderate or severe endometriosis whose symptoms are unrelieved by pharmacologic treatment, or for women who are older, surgery may be the most appropriate therapy. Conservative surgery attempts to eradicate visual signs of endometriosis and adhesions, eliminate symptoms of CPP, and restore the pelvic anatomy to a normal condition.²² However, because surgery cannot eliminate all microscopic endometrial implants, the disease may progress and symptoms may recur. For women with severe persistent endometriosis, the only treatment option may be a hysterectomy with bilateral salpingo-oophorectomy.

OVERVIEW OF IC

Patients with IC may present with a range of symptoms, including pelvic or suprapubic pain, urinary urgency/

frequency, nocturia, and dyspareunia.²⁷ Pelvic pain is the most characteristic symptom of IC.²⁸ Approximately 15% of patients with IC first present with pain in the absence of urologic symptoms.²⁷ Dyspareunia is not uncommon, and symptoms often flare after sexual intercourse.²⁹ Symptoms are also affected by the menstrual cycle and may become more pronounced before the onset of menstruation.^{28,30} The term interstitial cystitis/painful bladder syndrome (IC/PBS) is intended to encompass a broader symptomatic definition,^{31–33} and is recognized by the National Institute of Diabetes and Digestive and Kidney Diseases.³³

The pathogenesis of IC is not clearly understood; however, several hypotheses have been advanced to account for the condition. One of the most widely accepted theories suggests that the bladder urothelium is defective. The inner wall of the bladder is covered by a glycosaminoglycan-containing mucous layer. This layer protects the bladder by preventing infectious organisms from adhering to the epithelium and by prohibiting the entrance of irritating urinary solutes into the interstitium.³⁴ In patients with IC, this protective layer is defective, allowing solutes like urinary potassium to penetrate or leak into the mucosal layer.¹⁵ This can lead to activation of C-fibers, release of substance P, and mast cell degranulation, causing further injury and triggering the symptoms of urinary urgency/frequency and pelvic pain.³⁰

Given the similarities between endometriosis and IC—nonspecific symptomatology, as well as pain in the absence of other symptoms—it is critical that gynecologists consider IC as a diagnostic possibility when a patient initially presents with symptoms of CPP. Endometriosis is frequently asymptomatic.²² Even if endometriosis is confirmed by biopsy in a patient with CPP, it should not be assumed to be the only cause of pain, because it is common for patients with CPP to have multiple pain generators.

Consider IC in CPP Patients Refractory to Treatment for Endometriosis

It is not uncommon for endometriosis to recur after surgery; however, this often does not take place for years. Wheeler and Malinak³⁵ reported on a study of 423 patients who had undergone conservative surgery for endometriosis. The annual rate of recurrence for biopsy-confirmed endometriosis ranged from only 0.9% in the first postoperative year to 13.6% in the eighth year.³⁵ Therefore, if symptoms recur within the first 12 months after surgical therapy, IC should be considered as a possible cause and recurrent endometriosis is unlikely.

When therapy for the symptoms of endometriosis is unsuccessful, increasing evidence suggests that IC may be an underlying cause. Interstitial cystitis may be the sole cause of symptoms, or occur concurrently with other causes such as endometriosis or myofascial pain. In one study by Clemons et al,¹⁸ 45 women scheduled to undergo diagnostic laparoscopy for CPP were also evaluated with cystoscopy. Interstitial cystitis was diagnosed in 17 (38%) patients and endometriosis in 21 (47%). Of the 21 patients diagnosed with endometriosis, 7 (33%) also had IC.¹⁸

In a separate study conducted by Chung et al¹⁹ at a regional center specializing in CPP, 178 women presenting with chronic pelvic pain and uterine and bladder/anterior vaginal wall pain upon physical examination were evaluated using both laparoscopic and cystoscopic procedures.¹⁹ Irritative voiding symptoms were reported by 145 (81%) patients. Laparoscopy confirmed that 134 (75%) patients had biopsy-proven endometriosis, and cystoscopy confirmed that 159 (89%) had IC (**Table 1**). Both endometriosis and IC were diagnosed in 115 (65%) patients.¹⁹

Similar results were reported in a study by Paulson and Delgado²⁰ Of 35 women with CPP who underwent laparoscopy and cystoscopy with hydrodistension, 28 (80%) had IC; 28 (80%) had endometriosis; 24 (69%) had both diseases concurrently; and 32 (91%) had diagnoses of either IC, endometriosis, or both (**Table 2**).²⁰ The majority of patients (61%) complained of lower urinary tract symptoms in addition to pelvic pain.

Although the rates of IC in these studies vary widely, they indicate that many women with CPP may have IC alone or concurrently with endometriosis. No known causal relationship exists between endometriosis and IC, in part because the origin of both conditions is poorly understood. It is speculated that both diseases are caused by autoimmune disorders, with an unknown factor acting as a trigger for one or both.²⁰ Another possible explanation is

Table 1.
Pathology Among 178 Patients Chronic Pelvic Pain¹⁹

Pathology	Number	Percentage
Interstitial cystitis (IC)	159	89%
Endometriosis	134	75%
IC and endometriosis	115	65%
IC alone	44	25%
Endometriosis alone	19	11%

Table 2.
Pathology of 35 Patients With Chronic Pelvic Pain²⁰

Pathology	Number	Percentage
Interstitial cystitis (IC)	28	80%
Endometriosis	28	80%
IC and endometriosis	24	69%
IC or endometriosis*	32	91%
Adhesions	11	30%
Other pathology†	3	9%

*Includes patients with only one condition or with both.

†2 patients had an ovarian cyst, and 1 had ovarian remnant syndrome. Adapted with permission from Paulson JD, Delgado M. Chronic Pelvic Pain: the Occurrence of Interstitial Cystitis in a Gynecological Population. *JLSLS*. 2005;9:426–430.

that neuropathic upregulation leads to neurogenic inflammation and viscerovisceral hyperalgesia, in which chronic noxious stimuli at one site can contribute to referred pain and inflammation at other visceral organs.^{6,20,36} Pelvic organ cross-talk is important in the various functions of the pelvic organs (eg, storage, elimination, and sexual function), yet when alterations in these neural pathways as a result of disease or injury occur, these shared pathways result in pelvic organ cross-sensitization. This explains why patients often have multiple CPP disorders simultaneously (eg, IC, inflammatory bowel disease (IBS), vulvodynia, or dysmenorrhea). This concept of viscerovisceral cross-sensitization has repeatedly been demonstrated in the laboratory and is nicely reviewed by Ustinova.³⁷

DIAGNOSTIC EVALUATION OF POTENTIAL IC

As noted, IC can be difficult to distinguish from disorders like endometriosis.²⁵ Gynecologists, who see more women with CPP than other specialists, should be aware of the symptom overlap between IC and endometriosis and should screen patients with pelvic pain for IC.²⁵ When a patient presents with symptoms typically attributed to endometriosis, or with unresolved endometriosis, the following diagnostic approach may help determine whether IC is a contributing factor.

History and Physical Examination

A thorough history and physical examination are critical for an evaluation of any patient who presents with CPP. During the history, it is important to ask about the onset of

symptoms and the extent and location of the pain (in IC, pain usually worsens as the bladder fills and improves after voiding). Details on voiding symptoms, such as urgency, hesitancy, and/or frequency, should be determined as well.³⁰

A physical examination should be performed to evaluate for tenderness and to determine whether the tenderness elicited reproduces the pain that the patient typically experiences.¹ In patients with IC, a pelvic examination will often reveal tenderness of the bladder base, even upon gentle palpation.²⁸ A commonly overlooked finding in patients with CPP is levator muscle spasm and its associated myofascial pain.³⁸ The examination should also rule out vaginitis and other pelvic pathology.²⁸

A urinalysis and urine culture should be performed to detect the presence of infection or hematuria. Patients with IC may also have a concurrent bladder infection that requires diagnosis and treatment.^{28,39} Additional tests such as a urine cytology may be helpful in excluding other potential diagnoses (ie, bladder cancer or carcinoma in situ).²⁸

Symptom screening tools are useful because they can quantify behaviors that are associated with IC. They can also identify symptoms like dyspareunia that patients might not associate with their bladder symptoms and therefore may not report. A 24-hour voiding diary should be used to assess urinary frequency, nocturia, and fluid intake.²⁸ Healthy patients average 6.5 voids per day, whereas patients diagnosed with IC may on average experience 16.5 voids daily.³⁰ Voided volume is also important. Normal volume is 240mL to 300mL; an urge to void at 120mL or less should be considered abnormal.

The Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale is a questionnaire that screens for urinary urgency/frequency behaviors associated with IC, as well as pelvic pain and dyspareunia.⁴⁰ Studies show that PUF scores correlate with the likelihood of a positive PST, which is an indicator of IC.^{40,41}

Tests such as the PST and intravesical anesthetic challenge are being used with increasing frequency to help establish a diagnosis of IC.^{17,42} The PST involves instillation first of sterile water, and then of a potassium chloride solution into the bladder to assess evoked symptoms of pain and urgency. Patients without IC should not experience these symptoms in response to either solution. In contrast, approximately 80% of patients with IC have a positive response to instillation of the potassium chloride solution.^{15,16} Intravesical instillation of an anesthetic solution is

another diagnostic option. If the pain subsequently abates, often for a few days, it can be assumed that the bladder is its source. Most patients with IC have a positive response to this anesthetic challenge test, which suggests that it may be a useful diagnostic tool for IC.⁴²

Cystoscopy with hydrodistension of the bladder with the patient under general or conduction anesthesia is another tool to aid in the diagnosis of IC. Hydrodistension of an IC bladder may reveal glomerulations or Hunner's ulcers, as well as decreased bladder capacity.²⁸ However, these findings are not required for the diagnosis of IC. Hunner's ulcers are seen in approximately 4% of women with IC,⁴³ and many patients with symptoms consistent with IC have a negative cystoscopy.⁴⁴ Glomerulations have also been observed upon hydrodistension in asymptomatic women undergoing tubal ligation.^{43,45} Thus, false-negatives and false-positives are seen with cystoscopy. Cystoscopy may be necessary to rule out bladder cancer in patients who have gross or microscopic hematuria, are over 40 years old, have a history of tobacco use, or have occupational or other risk factors.^{36,43} In addition to its diagnostic value, hydrodistension has been shown to improve the symptoms of IC in 30% to 60% of patients, with relief lasting for up to several months.^{28,30}

MANAGING THE PATIENT WITH IC

Most experts in IC use a multimodal approach to therapy. In addition to pharmacologic agents, patients will often benefit from nonpharmacologic approaches, such as diet modification and physical therapy.

Pharmacologic Approaches

Pentosan polysulfate sodium (PPS) (ELMIRON, Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ) is the only oral therapy approved by the Food and Drug Administration (FDA) for the relief of bladder pain or discomfort associated with IC.^{46,47} This agent is a heparin-like compound similar in chemical structure to naturally occurring glycosaminoglycans and is believed to reinforce the protective mucosal lining of the bladder, thereby preventing irritants from entering the interstitium. Pentosan polysulfate sodium may also inhibit mast cell degranulation.⁴⁶ It has been proven effective for symptom relief in multiple studies.⁴⁷⁻⁵¹ The recommended dose of PPS is 100mg tid taken 1 hour before or 2 hours after meals. Some patients experience reduced symptoms within 4 weeks⁵²; however, others may require 3 to 6 months of therapy to notice an improvement in symptoms.⁴⁷ Generally, the longer the patient has symptoms, the longer it may take for these

symptoms to resolve. Pentosan polysulfate sodium is well tolerated. In clinical trials, the most frequently reported side effects in subjects taking recommended doses of PPS were blood in the stool (6.3%), diarrhea (4%), nausea (4%), hair loss (4%), headache (3%), rash (3%), upset stomach (2%), abdominal pain (2%), liver function abnormalities (1%), and dizziness (1%).

Dimethyl sulfoxide (DMSO), an antiinflammatory analgesic with muscle relaxant properties, is the only FDA-approved bladder instillation therapy for IC. Although its mechanism of action is not known, DMSO is thought to increase bladder capacity, inhibit mast cell degranulation, and modulate neural activity in the bladder.⁴⁶ Instillation therapy with DMSO can be administered every 1 to 2 weeks in cycles of 6 to 8 weeks. Patients comfortable with self-catheterization can perform this procedure at home, as needed.⁴⁶ Dimethyl sulfoxide is well tolerated but may leave a garlic-like taste and odor on the patient's breath and skin for up to 3 days after treatment. Blood tests, including liver function and kidney function, should be performed every 6 months.⁴⁶ Several trials have demonstrated that DMSO can provide moderate relief of symptoms, as well as increase bladder capacity for many patients with IC.^{46,53-55}

Various adjunctive therapies can be prescribed, as needed, to help provide relief from pain and other symptoms associated with IC, although these agents are not FDA approved for use in this patient population. Tricyclic antidepressants such as amitriptyline may be useful in IC. These drugs inhibit the secretion of histamine and block the reuptake of norepinephrine and serotonin in both the peripheral and central nervous system, which helps to mitigate pain. In addition, amitriptyline has anticholinergic effects that reduce urinary frequency and sedative effects that help with sleep disturbances and reduce nocturia.³⁶

Other therapies reported to be useful include antihistamines such as hydroxyzine and anticonvulsants such as gabapentin.³⁶

Nonpharmacologic Approaches

Strong anecdotal evidence suggests that diet modification offers some benefit to patients with IC. The elimination of certain foods may help to control symptoms and avoid flare-ups of the disease. Foods to avoid include chocolate, caffeine, spicy foods, and foods high in acidity, including tomatoes and citrus fruits and juices. Artificial sweeteners and cigarette smoking also appear to exacerbate symptoms of IC. Food diaries can help to identify foods and

beverages that act as triggers as well as those that are well tolerated.^{46,56}

Patients with IC should attempt to improve their lifestyle, exercise, and use stress-reduction strategies, all of which are thought to contribute to a better overall quality of life.⁵⁷ Bladder training may also be of value. Patients with IC can be taught to schedule voids, gradually increasing the time interval to 3 to 4 hours.⁴⁶

CONCLUSION

Patients with CPP may have endometriosis, IC, or both. Because the symptoms of these diseases overlap considerably, gynecologists should focus on the bladder as a potential source of symptoms. Any patient who presents with pelvic pain or has unresolved “endometriosis pain” should be evaluated for IC. Successful management of patients with CPP must involve the identification of all pain generators. If endometriosis is found, the clinician must still look for additional causes of visceral pain. Pain control is more likely to occur when all sources of pain are treated, including IC, irritable bowel syndrome, myofascial pain, and vulvodynia. Gynecologists can successfully manage CPP by screening for IC-related symptoms, making an early diagnosis, and initiating appropriate therapy and follow-up.

References:

1. Howard FM. Chronic pelvic pain. *Obstet Gynecol.* 2003;101:594–611.
2. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin. Medical management of endometriosis. Number 11, December 1999 (replaces Technical Bulletin Number 184, September 1993). Clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet.* 2000;71:183–196.
3. Ling FW, for the Pelvic Pain Study Group. Randomized controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol.* 1999;93:51–58.
4. Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. *Fertil Steril.* 1991;55:759–765.
5. Carter JE. Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain. *J Am Assoc Gynecol Laparosc.* 1994;2:43–47.
6. Stanford EJ, Koziol J, Feng A. The prevalence of interstitial cystitis, endometriosis, adhesions, and vulvar pain in women

with chronic pelvic pain. *J Minim Invasive Gynecol.* 2005;12:43–49.

7. ACOG Committee on Practice Bulletins—Gynecology. ACOG practice bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 51, March 2004. Chronic Pelvic Pain. *Obstet Gynecol.* 2004;103:589–605.
8. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. *Obstet Gynecol.* 1996;87:321–327.
9. Jamieson DJ, Steege JF. The prevalence of dysmenorrhea, dyspareunia, pelvic pain, and irritable bowel syndrome in primary care practices. *Obstet Gynecol.* 1996;87:55–58.
10. Reiter RC. A profile of women with chronic pelvic pain. *Clin Obstet Gynecol.* 1990;33:130–136.
11. Howard FM. The role of laparoscopy in chronic pelvic pain: promise and pitfalls. *Obstet Gynecol Surv.* 1993;48:357–387.
12. Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH. Patterns of diagnosis and referral in women consulting for chronic pelvic pain in UK primary care. *Br J Obstet Gynaecol.* 1999;106:1156–1161.
13. Zondervan KT, Yudkin PL, Vessey MP, et al. Chronic pelvic pain in the community—symptoms, investigations, and diagnoses. *Am J Obstet Gynecol.* 2001;184:1149–1155.
14. Chung MK. Interstitial cystitis in persistent posthysterectomy chronic pelvic pain. *JLSL.* 2004;8:329–333.
15. Parsons CL, Greenberger M, Gabal L, Bidair M, Barne G. The role of urinary potassium in the pathogenesis and diagnosis of interstitial cystitis. *J Urol.* 1998;159:1862–1867.
16. Parsons CL. Prostatitis, interstitial cystitis, chronic pelvic pain, and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. *Urology.* 2003;62:976–982.
17. Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ. Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity. *Obstet Gynecol.* 2001;98:127–132.
18. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. *Obstet Gynecol.* 2002;100:337–341.
19. Chung MK, Chung RP, Gordon D. Interstitial cystitis and endometriosis in patients with chronic pelvic pain: the “evil twins” syndrome. *JLSL.* 2005;9:25–29.
20. Paulson JD, Delgado M. Chronic pelvic pain: the occurrence of interstitial cystitis in a gynecological population. *JLSL.* 2005;9:426–430.

21. Sircus SI, Sant GR, Ucci AA Jr. Bladder detrusor endometriosis mimicking interstitial cystitis. *Urology*. 1988;32:339–342.
22. Memarzadeh S, Muse KN Jr., Fox MD. Endometriosis. In: DeCherney AH, Nathan L, eds. *Current Obstetric & Gynecologic Diagnosis & Treatment*. 9th ed. New York, NY: Lange Medical Books/McGraw-Hill; 2003;767–775.
23. Walter AJ, Hentz JG, Magtibay PM, Cornella JL, Magrina JF. Endometriosis: correlation between histologic and visual findings at laparoscopy. *Am J Obstet Gynecol*. 2001;184:1407–1413.
24. Khan N, Carr BR. Endometriosis, part 2: treatment options. *Female Patient*. 2004;29:26–33.
25. Lentz GM, Bavendam T, Stenchever MA, Miller JL, Smallbridge J. Hormonal manipulation in women with chronic, cyclic irritable bladder symptoms and pelvic pain. *Am J Obstet Gynecol*. 2002;186:1268–1273.
26. Mathias JR, Clench MH, Abell TL, et al. Effect of leuprolide acetate in treatment of abdominal pain and nausea in premenopausal women with functional bowel disease: a double-blind, placebo-controlled, randomized study. *Dig Dis Sci*. 1998;43:1347–1355.
27. Driscoll A, Teichman JMH. How do patients with interstitial cystitis present? *J Urol*. 2001;166:2118–2120.
28. Metts JF. Interstitial cystitis: urgency and frequency syndrome. *Am Fam Physician*. 2001;64:1199–1206, 1212–1214.
29. Parsons CL, Zupkas P, Parsons JK. Intravesical potassium sensitivity in patients with interstitial cystitis and urethral syndrome. *Urology*. 2001;57:428–433.
30. Dell JR. Chronic pelvic pain of bladder origin: a focus on interstitial cystitis. *Int J Fertil*. 2003;48:154–162.
31. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Am J Obstet Gynecol*. 2002;187:116–126.
32. Hanno P, Keay S, Moldwin R, Van Ophoven A. International Consultation on IC - Rome, September 2004/Forging an International Consensus: progress in painful bladder syndrome/interstitial cystitis. Report and abstracts. *Int Urogynecol J Pelvic Floor Dysfunct*. 16(suppl 1):S2–S34, 2005.
33. Interstitial cystitis/painful bladder syndrome. Bethesda, Md: National Kidney and Urologic Diseases Information Clearinghouse; June 2005. NIH Publication 05–3220. Available at: <http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis>. Accessed June 15, 2006.
34. Parsons CL. The therapeutic role of sulfated polysaccharides in the urinary bladder. *Urol Clin North Am*. 1994;21:93–100.
35. Wheeler JM, Malinak LR. Recurrent endometriosis: incidence, management, and prognosis. *Am J Obstet Gynecol*. 1983;146:247–253.
36. Butrick CW. Interstitial cystitis and chronic pelvic pain: new insights in neuropathology, diagnosis, and treatment. *Clin Obstet Gynecol*. 2003;46:811–823.
37. Ustinova EE, Fraser MO, Pezzone MA. Colonic irritation in the rat sensitizes urinary bladder afferents to mechanical and chemical stimuli: an afferent origin of pelvic organ cross-sensitization. *Am J Physiol Renal Physiol*. 2006;290:F1478–F1487.
38. Butrick CW. Discordant urination and defecation as symptoms of pelvic floor dysfunction. In: Howard FM, Perry CP, Carter JE, El-Minawi AM, Li R-Z, eds. *Pelvic Pain: Diagnosis and Management*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2000;279–299.
39. Nickel JC. Interstitial cystitis: characterization and management of an enigmatic urologic syndrome. *Rev Urol*. 2001;4:112–121.
40. Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology*. 2002;60:573–578.
41. Rosenberg MT, Page S, Roth L, Areaux D, Thallman C, Kval TE. A proactive approach to early identification and treatment in interstitial cystitis patients in a primary care setting. Presented at: Society for Infection and Inflammation in Urology Symposium at the American Urological Association Annual Meeting; May 8–13, 2004; San Francisco, California.
42. Moldwin R. The use of intravesical anesthetics to aid in the diagnosis of interstitial cystitis. Presented at: Research Insights Into Interstitial Cystitis: A Basic and Clinical Science Symposium; October 30–November 1, 2003; Alexandria, Virginia.
43. Ottem DP, Teichman JMH. What is the value of cystoscopy with hydrodistension for interstitial cystitis? *Urology*. 2005;66:494–499.
44. Erickson DR, Tomaszewski JE, Kunselman AR, et al. Do the National Institute of Diabetes and Digestive and Kidney Diseases cystoscopic criteria associate with other clinical and objective features of interstitial cystitis? *J Urol*. 2005;173:93–97.
45. Waxman JA, Sulak PJ, Kuehl TJ. Cystoscopic findings consistent with interstitial cystitis in normal women undergoing tubal ligation. *J Urol*. 1998;160:1663–1667.
46. Dell JR, Parsons CL. Multimodal therapy for interstitial cystitis. *J Reprod Med*. 2004;49:243–252.
47. ELMIRON® (pentosan polysulfate sodium) capsules prescribing information. Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; August 2004.
48. Mulholland SG, Hanno P, Parsons CL, Sant GR, Staskin DR. Pentosan polysulfate sodium for therapy of interstitial cystitis: a double-blind placebo-controlled clinical study. *Urology*. 1990;35:552–558.

49. Parsons CL, Mulholland SG. Successful therapy of interstitial cystitis with pentosanpolysulfate. *J Urol.* 1987;138:513–516.
50. Hanno PM. Analysis of long-term Elmiron therapy for interstitial cystitis. *Urology.* 49(suppl 5A):93–99, 1997.
51. Nickel JC, Barkin J, Forrest J, et al. , on behalf of the Elmiron Study Group. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium for interstitial cystitis. *Urology.* 2005;65:654–658.
52. Nickel JC, Barkin J, Forrest J, et al , for the Elmiron Study Group. Randomized, double-blind, dose-ranging study of pentosan polysulfate sodium (PPS) for interstitial cystitis (IC). *J Urol.* 2001;1:165(suppl):67.
53. Stewart BH, Shirley SW. Further experience with intravesical dimethyl sulfoxide in the treatment of interstitial cystitis. *J Urol.* 1976;116:36–38.
54. Stout L, Gerspach JM, Levy SM, et al. Dimethyl sulfoxide does not trigger urine histamine release in interstitial cystitis. *Urology.* 1995;46:653–656.
55. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol.* 1988;140:36–39.
56. Treatment options: IC and diet. Available at: <http://www.ichelp.org/TreatmentAndSelfHelp/ICAndDiet.html>. Accessed July 20, 2006.
57. Selo-Ojeme DO, Onwude JL. Interstitial cystitis. *J Obstet Gynaecol.* 2004;24:216–225. Vol. 11, No. 2