Interventional Therapies for Controlling Pelvic Pain: What is the Evidence?

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Abstract Chronic pelvic pain (CPP) has many potential causes and is often a complex disorder with multiple contributing etiologies. The evaluation and treatment of women with CPP often requires a multidimensional approach. The treatment of CPP consists of two approaches: 1) treatment of pain itself or global treatment, and 2) treatment of disease-specific etiologies. Most often, treatment requires a combination of both approaches. This article reviews recent literature in the global treatment of CPP, including pharmacologic, psychotherapy, and neuro-ablative, as well as specific interventions for endometriosis, interstitial cystitis, pelvic adhesive disease, adenomyosis, and pelvic venous congestion.

Keywords Pelvic pain · Visceral pain · Chronic pain · Neuroablation · Endometriosis · Adhesions · Adenomyosis · Pelvic congestion · Interstitial cystitis · Spinal cord stimulation · Peripheral nerve stimulation

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Introduction

Definition and Epidemiology

Chronic pelvic pain (CPP) is defined as pain of at least 6 months' duration that occurs in the lower abdomen or below the umbilicus and has resulted in functional or psychological disability or required intervention and treatment. The pain may be recurring or constant.

Estimating the prevalence of CPP is challenging in part due to the lack of consensus in the definition of CPP among investigators, and due to the estimate that only one third of women with CPP seek medical care [1, 2]. Studies have quoted the range to be anywhere from 4% to 40% [1–4]. Even with a likely underestimation of prevalence, CPP accounts for 10% of all ambulatory referrals to gynecologists, and greater than 10% of indications for hysterectomy [5]. This yields 881.5 billion dollars in health care costs in the United States per year [4].

Causes

The consensus definition of CPP is quite broad and falls short of defining the specific causes and manifestations of CPP [3]. CPP has many potential causes and is often a

complex disorder with multiple contributing etiologies. Women may have more than one condition; in fact, women with more than one medical condition tend to have greater pain than women with one disorder [6]. The evaluation and treatment of women with CPP often requires a multidimensional approach given the context of a complex overlap of possible etiologies. In some women, no etiology is ever found.

Therapeutic Interventions

As described by Fred Howard in an excellent 2003 review on CPP, therapeutic interventions center around two approaches: 1) treatment of CPP as a diagnosis in and of itself, and 2) treatment of specific disorders that may be contributing to CPP [7]. These two approaches could also be described as global versus disease-specific. A multidisciplinary approach is needed for diagnosis, but a multimodal approach involving both treatment approaches is often most effective for symptomatic relief. This article reviews the evidence for global interventions and disease-specific interventions for endometriosis, interstitial cystitis, pelvic adhesive disease, adenomyosis, and pelvic venous congestion. Other well-studied etiologies that are not specifically addressed in this review include irritable bowel syndrome, pelvic floor myalgia, and neuralgias.

Nonspecific Global Interventions

Howard [7] further classifies the global treatment of CPP into three categories: pharmaceutical, psychological, and neuroablative.

Pharmaceutical

Analgesics

Analgesics are the mainstay of treatment of chronic pain and include peripherally acting and central acting agents. Agents that act primarily peripherally include NSAIDs, acetaminophen, and aspirin. Those that target primarily central mechanisms are represented by the opioid class of medications. A 2009 review by Kroenke et al. [8••] outlined an evidence-based approach to the pharmacotherapy of chronic pain. NSAIDs are considered first-line treatment of CPP, particularly in suspected cases of endometriosis, and have been proven clinically effective [8••]. Tramadol is another analgesic often used and proven effective in the treatment of pain but carries a low risk of potential abuse. The abuse liability for this agent falls between that of NSAIDs and opioids (0.7%–2.7%) [9, 10]. Tramadol also carries a risk of seizures in patients with a prior history of

seizures and those taking a selective serotonin reuptake inhibitor (SSRI), tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or other opioids, which further limits its applicability. Opioids may allow the return of normal function in patients who have failed other analgesics, and produce tolerance, dependence, and possible addiction. Patient-informed consent agreements, scheduled doses in contrast to "as needed" dosing, frequent follow-up, and referral to pain specialists are tools to minimize inappropriate use of narcotics [7, 8••]. With respect to long-acting opioids, an evidence-based review concluded that there is insufficient evidence to suggest that one long-acting opioid is superior to another in the treatment of pain [10]. Methadone is more frequently being used for the treatment of noncancer pain, but data are limited to case series and a single small randomized trial.

Antidepressants

TCAs have the longest clinical record in the antidepressant class for the treatment of pain conditions. In a meta-analysis including 55 TCA trials, 76% showed benefit in patients with somatic symptoms, including pain [11]. Side effects include cardiovascular effects, falls, and potential lethal overdose. In the same study, TCAs were shown to be superior to SSRIs. Recent studies have demonstrated conflicting results for SSRIs in the treatment of pain. Duloxetine, a serotonin norepinephrine reuptake inhibitor (SNRI), has proven superior to placebo in three randomized, placebo-controlled trials in patients with pain due to diabetic peripheral neuropathy. However, two 2008 meta-analyses reported a statistically nonsignificant analgesic effect for duloxetine [12]. Venlafaxine, another SNRI, has also been shown to be superior to placebo in diabetic neuropathy and has been used in other painful conditions (although without approval from the US Food and Drug Administration [FDA]). An openlabel trial of citalopram (SSRI) in 2008 demonstrated a statistical trend toward improvement in pain intensity in women with CPP and appeared minimally effective in reducing disability [13]. Antidepressants are most commonly used in the context of multimodal treatment for pain and comorbidities such as depression or anxiety [14].

Anticonvulsants

Anticonvulsants, along with antidepressants, also have a long clinical history in the treatment of chronic pain. Those most supported by clinical experience and in the scientific literature include gabapentin and pregabalin [8••, 15]. A recent prospective randomized trial compared the use of gabapentin and amitriptyline or a combination of the two in the treatment of CPP. Pain relief was significantly better in patients receiving gabapentin either alone or in combination

with amitriptyline than in those receiving monotherapy with amitriptyline [16].

Psychotherapy

Incorporation of psychotherapy as part of a multidisciplinary approach has been demonstrated to improve management of pelvic pain and other pain syndromes, although in many studies the effect is small [17, 18, 19••, 20]. Psychotherapy can be implemented in many forms, including counseling, group therapy, cognitive behavioral therapy, and biofeedback. A recent randomized controlled study evaluated the use of somatocognitive therapy in the treatment of pelvic pain. When combined with standard gynecologic care, somatocognitive therapy improved psychological stress, pain experience, and motor functions of women with CPP [21]. Cognitive behavioral therapy, alone or within the context of a pain rehabilitation program, has the greatest empirical evidence for success [21–23]. Although this intervention may be limited by cost or patient compliance or acceptance, psychological treatment may decrease suffering and disability in CPP patients [7].

Neuroablative and Neural Blockade

Neuroablative or neurolytic therapies refer to the intentional injury of a nerve or nerves with the intent of reducing pain. Physicians may offer nonsurgical neurolytic treatments with chemicals (alcohol or phenol), cryoablation, or thermocoagulation for the control of CPP. Many practitioners reserve these treatments for cancer-related pain because of the associated risks such as excessive neurologic injury (neuritis), damage to non-neural tissue, and spotty relief due to tumor or scar tissue. Nonetheless, neurolysis can provide effective analgesia and life-enhancing benefits when applied properly. Neurolytic techniques more effectively treat discrete, well-circumscribed pain that patients can identify easily (eg, hemithoracic pain from malignancy). Interestingly, visceral pain, often diffuse and vague, generally responds to neurolysis despite its broadly based clinical features. For instance, superior hypogastric plexus (SHP) neurolysis can effectively reduce pelvic pain due to visceral pelvic cancers. Empirical data suggest that visceral and somatic pain respond more favorably to neurolytic therapy than neuropathic pain. Neurolytic agents predominantly affect neuronal axons, not cell bodies; therefore, pain relief is temporary secondary to axonal regeneration and neural plasticity [24]. For chemical neurolysis, clinicians generally use phenol, absolute alcohol, or glycerin. Chemical neurolysis is preferred over other modalities for procedures that must disrupt diffuse neural networks such as the SHP.

Surgical techniques were initially developed to address pelvic pain by presacral neurectomy (eg, cutting or excising nerve fibers to interrupt neural input) via laparoscopy [24]; however; there can be numerous complications associated with this method, including injury to lymphatics [25], major vessels (eg, iliac vessels), bowel, bladder, and ureters, as well as the onset of increased pain [26, 27]. Laparoscopic presacral neurectomy is noted to be a difficult procedure; therefore, neurectomy may be more effectively replaced by chemical neurolysis performed either laparoscopically or percutaneously [24].

The percutaneous approach to the SHP was initially described by Plancarte et al. [28] in 1990 for the treatment of pelvic cancer pain. Since that time, SHP blocks/neurolysis have been successfully used for the relief of pain in both noncancer and cancer conditions [28–30]. Either fluoroscopic or CT-guided [30, 31] imaging can be selected for any of the common anatomic approaches to the SHP. Among the noncancer pain investigations, SHP blocks or neurolytics have demonstrated satisfactory relief in patients with endometriosis or CPP [29, 31]. In a large trial of 227 patients with pelvic pain secondary to gynecological, colorectal, or genitourinary cancer, 79% had a positive response to a diagnostic SHP block, and 72% reported effective pain relief and significant reduction in opioid consumption following neurolytic block [32]. At the 6-month follow-up, 69% of patients had continued pain relief with a 67% reduction in opioid use for pain control.

In a randomized controlled trial comparing neurolytic SHP with opioid therapy, neurolytic SHP was found to significantly reduce pelvic or abdominal cancer pain intensity, opioid consumption, and drug-induced adverse effects while enhancing quality of life [33].

The ganglion impar (GI) block was first described by Plancarte in 1990 for the treatment of intractable perineal cancer pain of sympathetic etiology [34]. The primary indications for this procedure are sustained visceral or sympathetically maintained perineal pain from cancer (eg, anal or rectal cancer) or noncancer (eg, coccydynia) origin. Neural blockade is performed for nonmalignant pain of the distal part of the rectum, anus, distal urethra, distal third of vagina, and vulva. Patients often complain of burning sensations and urinary and rectal urgency associated with GI dysfunction. In a study of nonmalignant pain, the effects of radiofrequency ablation of the GI produced a 50% decrease in pain scores with average duration of 2.2 months and no complications [35]. Moreover, two prospective studies have reported good efficacy of neurolytic blockade of the GI using 6% phenol for unremitting perineal pain due to cancer [34, 36].

Sequential neural blockade of the SHP or GI with local anesthetics in patients with visceral or sympathetically maintained pain may attenuate central sensitization resulting in prolonged relief. For instance, patients suffering from CPP associated with endometriosis, adhesions, inflammation, interstitial cystitis, irritable bowel syndrome, and chronic pain

related to the bladder, prostate, testes, uterus, ovaries, descending/transverse colon, vagina, rectum, postsurgical pelvic pain, or neoplasms of the pelvis should be considered candidates for SHP blockade. Afferent fibers innervating the pelvic viscera travel with the sympathetic nerves, trunks, ganglia, and rami; thus, a sympathectomy can produce analgesia from painful pelvic structures. SHP blocks can be used for either diagnostic or therapeutic purposes. For instance, the block can help differentiate between referred low back pain from chronic pelvic disease and low back pain from myofascial, facet, disc, or other primary lumbar pathology. Vaginal, vulvar, anal, and rectal pain of the perineum may be controlled by blocking the GI in selected patients.

Disease-Specific Interventions

Interventions for Endometriosis

Endometriosis, defined as the presence of endometrial tissue outside the uterine cavity, is thought to be among the most common causes of pelvic pain in women. It may be present in 70% of women with CPP, or up to 60% of women with dysmenorrhea [37••, 38]. Laparoscopy is considered the gold standard for confirming the diagnosis of endometriosis; however, empiric medical therapy is often pursued prior to surgical intervention in patients without evidence of ovarian endometriomas or advanced disease.

Medical

Medical interventions include combined oral contraceptives (either continuous or cyclic use), progestogens, danazol, and gonadotropin-releasing hormone (GnRH) agonists. The 2008 Fertility and Sterility Practice Committee Educational Bulletin reviewed available data on medical options for endometriosis pain; although all the above treatments have been shown to be effective, there is little evidence that one medical regimen is superior to another [37••]. Furthermore, many medical treatments are confounded by side effects and a significant placebo effect. Norethindrone acetate has been shown in a prospective pilot study to produce significant improvement in pain and some gastrointestinal symptoms related to colorectal endometriosis [39]. A 2009 review by Vercellini [40••] outlined the available data regarding pharmacotherapy for endometriosis and proposed a practical problem-oriented approach to treatment. Medical interventions that are still under investigation include GnRH antagonists, aromatase inhibitors, progestogen agonists, estrogen receptor agonists and modulators, antiangiogenics, anti-inflammatory drugs, and immune modulators [41]. Insufficient data exist regarding these modalities at this time, limiting their clinical use.

Medical therapy following surgical intervention has also been studied, with mixed results and a suggestion that greater improvement in pain symptoms may be achieved with follow-up therapy. The 2004 Cochrane review on the topic concluded that there was insufficient evidence to support benefit of pre- or postoperative use of medical therapy for endometriosis [42]. As noted in the 2008 Fertility and Sterility Practice Committee Educational Bulletin, the largest study to date looking at postoperative GnRH agonist treatment did not show statistically significant improvement in long-term pain symptoms, although there was a trend in that direction [37••]. Other effective treatment modalities that have been studied as postoperative adjuncts include danazol, progestogens, and the levonorgestrel-releasing intrauterine device.

Complementary and alternative medicine has also been a field of active study with regard to treatment of endometriosis pain. A 2009 Cochrane review article chronicled the utility of Chinese herbal medicines in treating endometriosis and found that administration of Chinese herbal medicine may have comparable benefits to conventional medical therapy with fewer side effects; however further well-designed studies are needed [43]. Acupuncture has also been investigated for the treatment of endometriosis pain with mixed results, and is also limited by lack of large randomized controlled studies. A recent randomized sham-controlled study in adolescents showed a statistically significant decrease in pain rating over a short-term interval in patients treated with traditional Japanese-style acupuncture [44].

Laparoscopic surgical therapy involving either excision or ablation has been found to be effective with respect to pain outcomes compared with diagnostic laparoscopy; however, it remains unclear which specific surgical procedure is most efficacious, as documented in a 2009 Cochrane review [45]. Both excisional and ablative therapies have been shown to be effective in reducing pain symptoms, although placebo effect of surgical intervention has also been estimated at 30% [46]. Laparoscopic treatment of an endometrioma has also been found to be effective. When examining excision of an endometrioma versus drainage and ablation of the cyst, both techniques have been shown to be effective in relieving pain symptoms, although significantly more recurrence is noted with the drainage and ablation technique [47]. As an adjunct procedure to treat pelvic pain associated with endometriosis, laparoscopic uterosacral nerve ablation does not provide added benefit [46]. As noted in the review article by Catenacci et al. [46], presacral neurectomy has been shown to have some benefit in relieving pain caused by endometriosis, particularly midline dysmenorrhea.

Despite surgical intervention, it is estimated that 20% of patients will undergo repeat surgery for pelvic pain within

2 years. Hysterectomy with or without ovarian conservation has also been shown to be effective for CPP as a long-term treatment, and is often pursued after initial conservative surgical approaches. Recurrence of endometriosis posthysterectomy may more commonly occur with ovarian conservation, although a retrospective review suggested that the difference in recurrence may be less dramatic in women under the age of 40 years [48]. Hormonal therapy for menopausal symptoms following hysterectomy with oophorectomy with cyclic estrogen and progesterone replacement was found to be associated with recurrence rate of 3.5% (versus 0% in controls) in one randomized trial following patients for 46 months [49]. The role of bowel resection in the treatment of patients with colorectal endometriosis is also an area of ongoing study; a recent retrospective study by Stepniewska et al. [50••] demonstrated a lower rate of recurrence in patients with bowel endometriosis who had undergone segmental resection.

Interventions for Interstitial Cystitis

Interstitial cystitis (IC) is a urologic cause of pelvic pain characterized by chronic inflammation of the bladder. The exact definition of this disorder is debatable, but the majority of diagnostic criteria include the following: 1) bladder pain, 2) urinary voiding symptoms (ie, urgency, frequency, nocturia), 3) characteristic findings at the time of cystoscopy (ie, glomerulations, Hunner's ulcerations), and 4) the absence of other conditions that could cause such symptoms [51–54]. The nomenclature assigned to IC is also constantly evolving. A change has been recently implemented by the European Society for the Study of Interstitial Cystitis to rename IC as *bladder pain syndrome* (BPS) to create a consensus definition and general set of diagnostic criteria. The exact pathophysiology behind this disease is poorly understood.

Dietary and Lifestyle Modifications

Avoidance of certain foods and beverages in combination with behavioral training and psychosocial support has been shown in the past to improve symptoms related to IC [55••]. A recent survey-driven study sought to define food products, beverages, and medicines that subjectively exacerbated IC symptoms. Food culprits included citrus fruits, tomatoes/tomato products, and foods containing hot pepper. Caffeine-containing, alcoholic, and carbonated beverages also exacerbated symptoms more than other drinks. Condiments such as artificial sweeteners, vinegar, monosodium glutamate, and horseradish were implicated as well. Aspirin, antibiotics, ibuprofen, and decongestants were further thought to worsen symptoms when administered [56••].

Medical Therapy

Multiple medical therapies have been studied for the management of IC and are often favored as a conservative measure of treatment. A 2007 review of pharmacologic management by Dimitrakov et al. [57••] highlighted the majority of oral treatment options and performed a specific analysis of studies looking at oral pentosan polysulfate (PPS), an FDA-approved treatment option. This meta-analysis favored treatment compared with placebo. Moreover, combination of PPS with low-dose subcutaneous heparin demonstrated superior outcomes versus PPS alone [58]. Studies on impact of hydroxyzine have demonstrated a beneficial effect, but are limited in power and study design, and as such further investigation is required [59]. Amitriptyline is thought to provide beneficial effects in treatment of IC via modulation of neuronal dysfunction [55••]. In one study, 64% of patients demonstrated improvement; however, use of amitriptyline was limited by side effects (84% of patients) [60]. Prednisone and cyclosporine have also been studied as immunosuppressive agents to reduce bladder inflammation in the management of IC. They are considered second-line agents associated with varied symptomatic relief and relatively few side effects [61–63].

Intravesical Treatments

In 2007, a Cochrane database review was conducted to explore current evidence on the use of intravesical treatments for IC. This review included multiple randomized controlled trials primarily evaluating the use of resiniferatoxin, dimethyl sulfoxide (DMSO), bacillus Calmette-Guérin (BCG), PPS, oxybutynin, and alkalinization of urine pH as forms of intravesical treatment. Data surrounding treatment modalities were mixed in the majority of cases, but the following was demonstrated [64••]:

- Resiniferatoxin, an agent causing desensitization of afferent bladder innervation, commonly caused pain with instillation and did not demonstrate significant differences in outcomes reported.
- DMSO, an intravesical therapy causing an anti-inflammatory response, analgesia, and muscle relaxation, had limited data but demonstrated no significant improvement in bladder pain and capacity compared with placebo.
- BCG, a likely immune-modulating agent, demonstrated decrease in pain in treated groups in two trials, but failed to demonstrate improved quality of life in the larger of the two trials. No significant increase in adverse events was seen with BCG therapy in either trial.
- PPS, which acts by reducing the permeability of the bladder wall to toxins, has limited data.

- Oxybutynin, an anticholinergic agent that reduces bladder spasm, showed promising results in increased bladder capacity and decreased urinary frequency when combined with bladder training, and compared with placebo intravesical treatment. Pain was not assessed in the study reviewed.
- Alkalinization of urine pH also showed limited data, but no significant advantages in treatment.

Hyaluronic acid (HA), heparin, and chondroitin have also been studied in the treatment of IC. All are components of the glycosaminoglycan (GAG) layer of the internal bladder wall, which is thought to malfunction in IC resulting in increased permeability and subsequent pain and urinary symptoms. Several studies have been performed specific to HA with mixed results. In 2008, Cervigni et al. [65] looked at the effect of a higher concentration of HA combined with chondroitin instilled in patients with refractory cases of IC. A statistically significant improvement was seen at 5 months as well as a significant reduction in hyperemia and submucosal vascular ectasia at cystoscopy. This study lacked power and placebo control but proposed a potentially promising therapy for refractory IC cases pending further investigation.

Intravesical PPS, as mentioned in the above Cochrane review, was studied recently in a prospective, uncontrolled study by Daha et al. [66], demonstrating an improvement in symptoms and quality of life. These effects were limited in duration, and most individuals required repeat treatments. Additional placebo-controlled, randomized trials are needed to determine true efficacy of this treatment.

Intravesical liposome is also being investigated as a bladder mucosal protective agent. Although the pilot study of this agent in humans lacked power and placebo control, reduction in symptoms in IC patients was similar to that with oral PPS, and side effects were minimal [67].

Botulinum toxin A has been used to manage different forms of muscular hypercontractility for many years and recently has been investigated for its potential analgesic effects when injected into the bladder wall. Several small studies have yielded conflicting results and recurrence of symptoms [68]. Repeat doses of botulinum toxin A have been proposed at 6-month intervals in order to maintain relief of symptoms. Incomplete bladder emptying secondary to decreased detrusor contractility is an adverse effect to be investigated in further trials of this drug therapy [69].

Bladder Hydrodistension

Bladder hydrodistension (HD) has both diagnostic and therapeutic purposes in the management of IC. Improvement in patient symptoms following HD has been documented for many years, but the duration of treatment effect appears to be limited [70]. In a recent study combining HD with bladder training, 51.2% of patients experienced remission of symptoms, suggesting that bladder training may significantly improve bladder capacity and subsequently, bladder functioning [71].

Nerve Stimulation

Neuromodulation via sacral nerve stimulation has been a therapy choice for patients with lower urinary tract dysfunction of multiple etiologies refractory to more conservative management for many years [72]. In the past 10 years, sacral nerve stimulation has been studied to some extent in management of refractory IC. In a multicenter trial, 33 patients underwent percutaneous sacral nerve root stimulation who would have otherwise been candidates for surgical reconstruction. Statistically significant differences were seen in pretreatment and treatment groups in reported pain, frequency, and voided volume, and minimal side effects were noted [73]. More recently, this technique has been applied for the treatment of CPP. In an observational study of 10 patients undergoing sacral nerve stimulation for intractable pelvic pain, nine reported a decrease in pain severity for at least 19 months [74]. In another study, 11 patients were followed for 36 months after undergoing sacral stimulator placement: nine experienced extended and significant reduction in their pelvic pain, and two failed the therapy soon after implantation [75]. This failure was likely due to a false-positive result during the trial. These studies suggest that sacral stimulation may be helpful in reducing pelvic pain among properly chosen patients who undergo a successful stimulator trial. There is emerging evidence that a midline dorsal column pathway exists that may mediate the perception of visceral pelvic pain; therefore, dorsal column stimulation may serve an effective means of treating CPP. In 2006, Kapural et al. [76] reported that six female patients with severe CPP undergoing dual lead implantation with lead tip between the levels of T11–T12 described significant improvement in pain scores and activities of daily living during an average follow-up of 2.6 years.

An additional study explored the utility of a permanent sacral nerve stimulator which also demonstrated improvement in symptoms, potentially greater than its percutaneous counterpart [77]. The most promising alternative to sacral stimulation appears to be chronic pudendal neuromodulation. In a recent study incorporating both IC and non-IC patients, 52% had previously undergone sacral stimulation, and among those patients, 93.2% responded to pudendal stimulation [78].

Surgical Interventions

Surgical options to manage IC are often used as a last resort. Transurethral resection of ulcers has been studied in the literature, but only following bladder HD [9]. In 2007,

long-term results of reconstructive surgery for BPS/IC were reviewed by Rössberger et al. [79]. Subtrigonal cystectomy and ileocystoplasty was the most prominently utilized method of reconstruction. Surgical interventions involve a greater risk of adverse events and are essentially irreversible, making patient selection and education paramount.

Interventions for Pelvic Adhesive Disease

An adhesion is defined as the abnormal union of two tissues that are normally separate, and may range from thin and filmy to dense fibrous bands. Risk factors for the development of pelvic adhesions include processes that result in intraperitoneal inflammation such as previous surgery, pelvic inflammatory disease, appendicitis, endometriosis, and inflammatory bowel disease. The relationship between pelvic adhesions and pain is poorly defined. The consensus opinion, as stated in the 2005 Cochrane Review, indicates that there is no evidence of benefit of adhesiolysis on improvement in CPP other than in women with severe adhesions [80]. This conclusion, however, is limited by lack of randomized controlled studies on the topic.

Recent studies that have looked at the role of adhesiolysis for chronic pain include a 2006 study by Keltz et al. [81], in which a group of 25 subjects who were scheduled to undergo laparoscopic surgery for CPP were randomly assigned to receive either additional right paracolic adhesiolysis or no additional procedure. All patients experienced a reduction in right lower quadrant tenderness postoperatively; however, the treatment group had a significantly greater reduction in right lower quadrant pain than the control group.

This topic continues to be fraught with controversy, as discussed in a 2009 commentary by Roman et al. [82••]. In this article, the authors stressed the need for further well-designed prospective randomized controlled studies on this topic and cautioned against changes in clinic practice based on the available data.

Interventions for Adenomyosis

Adenomyosis may result in chronic pain in the form of dysmenorrhea. The pain may persist or precede the menstrual cycle resulting in intermittent CPP. It is characterized by the growth of ectopic endometrial glands and stroma deep within the myometrium, which can lead to enlargement of the uterus due to reactive hyperplasia and hypertrophy of surrounding myometrium [83]. The disease could range from diffuse to small focal disease termed *adenomyomas*. Features of adenomyosis are found in 20% to 35% of hysterectomy specimens [84].

Hysterectomy is the only definitive treatment for debilitating adenomyosis. Studies on alternative treatments are hindered by a lack of consensus in pretreatment definitions and criteria. The current accepted MRI guideline for diagnosis is a junctional zone greater than 12 mm, with or without myometrial foci of high signal intensity. MRI is considered superior to ultrasound in the diagnosis of adenomyosis [85].

Medical Options

Medical options for treatment include progestins either in the oral or intrauterine device (IUD) form, oral contraceptive pills, GnRH agonists, or antiestrogens. In observational studies, GnRH agonists have demonstrated a decrease in the junctional zone width and transient amenorrhea and decrease in uterine size. Similar to the response in leiomyomas, discontinuation of GnRH results in a rebound effect with resumption of pretreatment uterine size and symptoms within 6 months of discontinuation. Use of oral contraceptive pills as follow-up to GnRH did not prevent recurrence of symptoms [83]. Randomized and controlled trials are lacking. Case series demonstrate evidence of high rates of improvement in menorrhagia and dysmenorrhea in women using the IUD, but criteria for IUD insertion and diagnosis of adenomyosis have not been consistent [84]. A retrospective study demonstrated superior results in women with adenomyosis treated with the combination of ablation and IUD compared with IUD alone (100% amenorrhea versus 10%) [84]. Small case series have demonstrated similar rates of improvement with use of a danazol IUD (81% improvement dysmenorrhea, 76% improvement menorrhagia), with no systemic side effects [84]. Similar to treatment of endometriosis, use of oral contraceptives or aromatase inhibitors may provide benefits for women with amenorrhea, but little data exist in their use in patients with adenomyosis.

Surgical Options

Conservative options for the treatment of adenomyosis consist of endometrial ablation and excision. Endometrial ablation may be successful in cases of superficial adenomyosis (< 2.5-cm depth). Case series of women undergoing hysteroscopic resection or third generation endometrial ablation have demonstrated successful rates of amenorrhea and relief of pelvic pain [83, 84]. In the past, endometrial ablation failures have been attributed to adenomyosis. However, the likelihood of recurrent symptoms correlated with depth of penetration of adenomyotic disease. Case series do suggest that ablation may be successful in properly selected patients [83, 84]. Surgical excision may be performed by laparotomy or laparoscopy. They consist of either myometrial reduction or removal of adenomyomata. Preoperative mapping is described using ultrasound

or MRI. Difficulties with these procedures include unclear borders of the adenomyomatous tissue in comparison to the clear margins typically seen with fibroids, risk of recurrence, risk of adhesions, and creating pockets of untreated adenomyosis when closing the myometrial defects. Surgical excision in conjunction with GnRH agonist has also been described. Adenomyotic nodules can also be found in the subserosa or retroperitoneal region and may be amenable to conservative excision [83, 84]. However, data on excision are limited to small case series only. Overall, well-designed randomized controlled trials of both medical and surgical treatments, including long-term outcomes such as fertility and pregnancy for the control of adenomyosis, are lacking.

Interventional Radiology

Radiology procedures consist primarily of MR-guided focused ultrasound (MRgFUS) and uterine artery embolization (UAE). A single case report describes the successful treatment of a single adenomyoma with MRgFUS. Menorrhagia improved, and the size of the lesion decreased by 50%. The patient proceeded to successful pregnancy. Available data are preliminary and limited, particularly with respect to fertility and pregnancy [86]. In a recent analysis of 20 cases of adenomyosis treated by MRgFUS, uterine volume was decreased at 6 months (12.7%), and clinical symptoms and severity scores also improved during the 6 months of follow-up [87]. UAE has been shown to be effective in larger case series, resulting in improvement in dysmenorrhea at 1 year and ranging from 57% to 80% improvement. However, failure rates may be as high as 17%, and recurrence rates approximate 5%. Time to recurrence ranged from 4 to 48 months [88]. Interestingly, clinical effectiveness did not differ between patients with diffuse or focal disease in one study. The mean follow-up time was 15 months [88, 89]. UAE remains an alternative to definitive treatment with hysterectomy, but counseling should include risk of failure.

Interventions for Venous Congestion

The diagnosis of pelvic congestion syndrome (PCS) secondary to pelvic varices remains controversial. Dilatation of the ovarian veins can result in vascular incompetence and retrograde blood flow. Dilated veins are more frequently present with increased parity, and PCS occurs more frequently in multigravid women [90]. It is characterized by deep dyspareunia, postcoital pain, and exacerbation of pain after prolonged standing [91]. The pain is often described as shifting. Ovarian tenderness may be elicited on examination. Diagnosis is characterized by radiographic findings of pelvic varicosities, although many varicosities are also seen in women without symptoms. Pelvic venography is favored over ultrasound and MRI for diagnosis because veins may be collapsed in the supine position. Direct visualization of tortuous and dilated ovarian veins by selective venography remains the gold standard for diagnosis [90]. However, noninvasive alternatives are increasingly used for initial assessment, particularly pelvic MRI. Treatment options for PCS include ovarian suppression or ligation, and embolization of veins [92]. Other treatments limited by observational data alone include hysterectomy and bilateral salpingo-oophorectomy, surgical ligation of veins, and sclerotherapy.

Medical Interventions: Ovarian Suppression

Medical interventions include anti-inflammatory agents, GnRH agonists, oral contraceptives, and synthetic progestins including medroxyprogesterone acetate (MPA), oral progestins, and etonogestrel, all of which are supported in the literature. Both oral MPA and depot goserelin have demonstrated improvement by venography and in pelvic pain; however, goserelin was statistically superior to MPA [93]. Interestingly, the combination of MPA with psychotherapy appears to delay recurrence of symptoms after discontinuation of treatment [94]. Finally, in a 2009 randomized trial of etonogestrel versus placebo in 25 patients, etonogestrel was associated with a decrease in pain, blood loss, and venography scores at 6 months. More than 80% of women reported satisfaction at 1 year [95].

Embolization

The role of embolization is supported by several published case series, with success rates in reduction of pelvic pain ranging from 50% to 80%. More recent literature supports success rates of 98% to 100%, with recurrence rates of less than 8% [90]. A 2007 case series of 24 patients treated by embolization demonstrated a mean clinical improvement of 80%, 77%, 80%, and 76% at respectively 45 days, 1-, 2-, and 3-year follow-up intervals after embolization [96]. Pain reduction has been demonstrated in one study up to 4 years after embolization [97].

Conclusions

CPP has many potential causes and is often a complex disorder with multiple contributing etiologies. The successful treatment of women with CPP often requires a multidimensional approach given the context of a complex overlap of possible etiologies. This may include global- or etiology-specific approaches, and either medical or interventional strategies (eg, surgery, radiology, nerve blocks). Typically, a combination of approaches yields the greatest symptomatic improvement.

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