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Pelvic pain in women and men: recent findings

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Purpose of review

All Pubmed-listed articles generated by the search terms 'pelvic' and 'pain' from the year 2004 (plus or minus 6 months) were examined for relevance to pain management therapeutics. An emphasis was given to clinical studies related to chronic pain disorders.

Recent findings

Use of the descriptive diagnosis 'pelvic pain', traditionally limited to gynecological pains, has now been generalized to include male populations with similar symptom complexes arising from organs of reproduction and other pelvic organ systems such as the gastrointestinal tract and urological structures. Clinical studies have sought to refine or test existing 'standard' therapies for current pain groupings, and have frequently obtained frustrating results because many therapies appear to be effective in only a subset of patients. Notably, the same therapeutics appear to be effective in similar subsets of patients with other protean disorders.

Summary

A commonality of symptoms suggests a commonality of pathophysiology, although this has not proved to be globally true. The success of therapeutic options appears to depend upon a stratification of previous pain groupings into overlapping subsets each with their effective treatment. Current studies are still defining these subsets and finding monotherapies to be inadequate for whole populations.

Keywords

endometriosis, interstitial cystitis, pelvic pain

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Abbreviations

APF	antiproliferative factor
CPPS	chronic pelvic pain syndrome
IBS	irritable bowel syndrome
NIDDK	National Institute of Diabetes, Digestive and Kidney diseases
PBS	painful bladder syndrome

0952-7907

Introduction

Pelvic pain is a descriptive diagnosis that has been traditionally associated with gynecological pains. In recent years, there has become an increasing appreciation of the high incidence of men with similar symptomatology. At the same time there has also been an increasing awareness of co-morbidities related to pelvic pain disorders. In some cases disorders previously viewed as co-morbidities are now being viewed as the morbidity. Some sources of pelvic pain are readily identified. Infections of the urogenital structures, cancer, structural or functional obstructions impeding the flow of urine, feces or other fluids, and inflammation caused by systemic diseases or local processes can all lead to pain localized to the pelvis, and have treatments related to the primary etiologies. Some disorders await definition of their pathology. One of these is chronic pelvic pain syndrome (CPPS), a diagnosis of exclusion in women that has been used to describe a symptom complex that does not have an identified pathophysiology. A male correlate to CPPS, prostatodynia, has recently been renamed 'male CPPS' because it is also a diagnosis of exclusion and forms a similar symptom complex to that experienced by women. Studies examining psychological factors related to pelvic/urogenital pain in men and women have found the sexes to be the same when it came to the impact of pain on their quality of life and affective measures such as depression or anxiety [1••]. CPPS has proved difficult to treat because treatment of a disorder of unknown etiology is driven by theory and empiric trial rather than by rational protocol.

The following paper will discuss recently published studies that are relevant to both the treatment and understanding of the pathophysiological mechanisms of pelvic pain. It consists of data gleaned from over a 1000 articles generated by a Pubmed search using the terms 'pelvic' and 'pain' and targeted at the time period of 2004 (plus or minus 6 months). Focused searches of the same time period for specific disorders supplemented the database. Pain caused by orthopedic, oncological or acute obstetric processes was not included except as it impacted the development of the other identified chronic processes.

Sources of pelvic pain in both sexes (but predominantly women)

Numerous structures reside within the pelvis that can be a source of pelvic pain. The main sources of pain are the genitourinary structures, the gastrointestinal tract and pelvic floor musculature. It is notable that although

disorders that involve these three sources are possible in both men and women, epidemiology related to the disorders suggests a profound female to male predominance. It is notable that certain 'diagnoses' involving the pelvic organs have become 'trendy' secondary to the use of broad non-specific criteria for symptom complexes or through the use of 'tests' that have only limited specificity. This has unfortunately served to muddle the minds of the public, some clinicians and some researchers so that 'diagnoses' that are actually descriptions of symptom complexes are used for studies, despite known subpopulations within that diagnosis that probably have differing pathophysiologies.

Interstitial cystitis

The urinary bladder has attracted particular attention as a source of pelvic pain because researchers and clinicians have approached the disease entity called interstitial cystitis with renewed vigor as a result of public interest and support. Once viewed as an obscure disease, some claim that 10–30% of the female population may have interstitial cystitis based on symptoms or non-specific tests [2•]. Clinicians associated with the United States' National Institute of Diabetes, Digestive and Kidney diseases (NIDDK) have defined stringent criteria for the diagnosis of interstitial cystitis, but acknowledge that there is value in examining the more generic painful bladder syndrome (PBS), a symptom complex that might lead to interstitial cystitis. The NIDDK research-related definition of interstitial cystitis has both inclusion and exclusion criteria based on cystoscopic, urodynamic and other laboratory tests, but PBS only requires the symptoms of frequency, urgency and pain. As many pelvic pain disorders have frequency and urgency associated with their other symptom complexes, there is a logical link formed to PBS. Stanford *et al.* [3•] found 69% of patients referred to their pelvic pain clinic demonstrated sensitivity to the intravesical administration of potassium and so could qualify as having PBS, but only 11% of the individuals met the cystoscopic criteria for interstitial cystitis.

Interstitial cystitis has recently been described as one of the 'evil twins' of chronic pelvic pain coupled with endometriosis. A recent study of 178 women with pelvic pain demonstrated cystoscopic evidence of interstitial cystitis, laparoscopic evidence of endometriosis or both in all subjects [4••]. A 'missed' diagnosis of interstitial cystitis has also been blamed for many cases of chronic pelvic pain after hysterectomy [5•]. Like many other patients with chronic pain disorders, individuals with interstitial cystitis are hypersensitive to multiple painful stimuli including bladder distension [6•]. Co-morbidities are common with interstitial cystitis [7•], and it has been proposed that interstitial cystitis and both female and male CPPS have similar pathophysiologies [8,9]. Evidence contrary to this assertion is given by a recent study in which urine markers that have been identified as specific for interstitial cystitis in women (i.e. antiproliferative factor; APF) were not found in men with CPPS unless they also had the other diagnostic criteria for interstitial cystitis [10••]. This suggests that there is, at best, only a partial overlap of the two disorders. Additional validity for urinary APF as a laboratory marker for interstitial cystitis was given by the confirmation of previous findings related to specificity from one laboratory in the United States [11] by an independent laboratory in China [12••]. The structure of APF has now also been described as a peptide in the Frizzled 8 family [13••].

In the United States a strong impetus for interstitial cystitis-related studies has been generated by the formation of the Interstitial Cystitis Clinical Trials Group (now the Interstitial Cystitis Clinical Research Network), a multicenter collaborative effort coordinated by the NIDDK, which has been responsible for the assessment of intravesical resiniferatoxin [14••], intravesical bacillus Calmette–Guerin [15••] and oral pentosan polysulfate with and without hydroxyzine [16] as treatments for interstitial cystitis. These studies enrolled large numbers of individuals and used appropriately controlled methodologies, but unfortunately failed to observe robust effects of any of these treatments over placebo in the interstitial cystitis group as a whole. The bacillus Calmette–Guerin study did achieve statistically significant effects in many of its secondary measurements and demonstrated a strong trend ($P = 0.062$) in its primary measures, but the other studies failed to achieve statistical significance in any of their major measures. Criticism of those studies has been related to the observation that the individuals who were typically enrolled were generally recalcitrant to treatment before involvement in the study.

'Standard' therapeutics related to interstitial cystitis still undergoing evaluation include the use of dietary supplements [17•], amitriptyline [18•], pentosan polysulfate sodium [19•], alkalinized urine [20••], bladder washes with local anesthetics/heparin [21], corticosteroids [22], and intravesical dimethyl sulfoxide [23]. Series reports or open-label trials suggest benefit from sacral nerve root stimulation [24–26], low-dose cyclosporine A [27•], hyperbaric oxygen [28•], intratrigonal botulinum toxin injections [29], prolonged infusions of resiniferatoxin [30•], but not from posterior tibial nerve stimulation intended to mimic acupuncture treatments [31,32•]. There exists, at present, no absolute standard-of-care for patients with the diagnosis of interstitial cystitis.

Irritable bowel syndrome

A highly prevalent disorder linking altered bowel habit with pain and producing profound deteriorations in quality of life [33•], irritable bowel syndrome (IBS) has frequently

been observed as a co-morbidity with other pelvic pain disorders [34••,35•,36,37•]. Hypersensitivity to cutaneous thermal stimuli has been noted in IBS patients, particularly in segmental dermatomes [38•], demonstrating a global sensory component to the pain syndrome. Menstrual cycle effects have previously been observed and 'standard' therapies include bulking agents, antispasmodic and antidepressant agents, although evidence for the benefit of these agents is weak [39]. Several new agents have recently received approval for use in differing forms of IBS. Tegaserod [40•], a 5HT4 receptor agonist, is used for constipation-type IBS in women, with a limited side-effect profile. Alosetron [41,42], a 5HT3 receptor antagonist, has demonstrated benefit for diarrhea-type IBS in women, also with apparent long-term efficacy. Although initial studies were most supportive of the use of alosetron in women, recent studies have also demonstrated benefit in men, but a single incidence of possible ischemic colitis that may have been caused by the drug raise some clinical concerns [43]. New drugs for IBS in clinical trials include a different 5HT3 receptor antagonist, cilansetron [44], and a kappa opioid receptor agonist, asimadoline [45], although formal efficacy studies are still lacking.

Pelvic floor musculature

Spasm or hypertonus of the muscles forming the floor of the pelvic basin have frequently been invoked as the etiology of pain syndromes [46•]. A common sign and symptom accompanying pelvic pain disorders [47•], increased muscle tone has been treated successfully with physical therapy [46•], and more recently with botulinum toxin injections [48•] as indicated by case/series reports.

Sources of pelvic pain in women

Pelvic pain in women is generally divided into those highly affected by the menstrual cycle (endometriosis and dysmenorrhea) and those less affected. Kuligowska *et al.* [49•] proposed that most forms of pelvic pain may be diagnosed non-invasively using imaging modalities such as high resolution magnetic resonance, with characteristic features notable for adenomyosis, endometriosis, pelvic vascular congestion, and other less common congenital or acquired abnormalities. Practice guidelines and treatment recommendations related to pelvic pain disorders have recently been published by the American [50,51] and European [52] organizations.

Approximately 75% of women experience menstruation-related pains in their reproductive years, with 5% of women experiencing pains sufficient to cause absence from work [53•]. Like other painful disorders, pelvic pains have been associated with increases in sensitivity in somatic structures, as was recently demonstrated by Bajaj *et al.* [54] for individuals with endometriosis. Previous pathology within the pelvis, such as pelvic inflammatory disease, is a predictor of future pelvic pain [55•]. Psychological factors also appear to contribute to the clinical presentation of pelvic pain [56,57•], and contribute to a lower quality of life [58]. The major forms of pelvic pain in women that have generated recent publications will be discussed below.

Endometriosis/dysmenorrhea

Pelvic pains that vary predominantly with the menstrual cycle are defined as dysmenorrhea, which may be primary (without other cause) or secondary to other definable causes, such as the presence of extrauterine endometrial tissue (endometriosis). It would appear that virtually all clinical pains in women, ranging from headache to IBS to fibromyalgia, are affected by the hormonal cycling associated with menstruation, and so the presence of a menstrual cycle effect alone does not absolutely indicate endometriosis or dysmenorrhea. A sensitivity to hormonal cycling does suggest that benefit might be gained from modulating hormones in these patients, and so much of the recent literature related to endometriosis and dysmenorrhea has been related to the refinement of hormonal therapies that lead to more benefit than side-effects [59,60•–62•,63,64••]. Other non-invasive treatments for dysmenorrhea/endometriosis that have been examined in open trials include the use of thermal biofeedback [65] and acupuncture [66]. Notably, a systematic review of the literature related to chiropractic spinal manipulation for dysmenorrhea found no definitive evidence of benefit [67••].

Surgical therapy for endometriosis has been a mainstay of treatment for many years. Abbott *et al.* [68••] recently compared early surgical excision with delayed surgical excision of endometrial lesions in a randomized, blinded fashion, and reported that the early treatment group were significantly improved over a group that only received a diagnostic laparoscopy. Although this does not directly compare against management with non-invasive means alone, most of the subjects had already 'failed' medical treatment. Yap *et al.* [69•], in a systematic review of studies related to hormonal therapy before or after endometrial surgery, were unable to determine whether the hormonal treatments were of benefit in those particular patients. Two different surgical groups reported on the potential benefits of the laparoscopic uterine nerve ablation technique. It is notable that one group [70••] only saw benefit in patients without endometriosis and the other group reported benefit specifically in subjects with endometriosis [71••]. Most concerning in the latter report was the presence of significant complications in the laparoscopic uterine nerve ablation groups.

Vulvodynia

Pain localized to the vulva can generally be dissociated from other pains felt more deeply within the pelvis. Twenty per cent of subjects presenting to a pelvic pain

clinic were found to have vulvar pain rather than pelvic pain as their main complaint [3•]. Co-morbidity with other painful disorders such as interstitial cystitis have been noted [72], but are uncommon. Simple treatments such as the overnight application of a 5% lidocaine ointment has proved of value in open trials [73]. Botulinum toxin injections into the pelvic floor musculature have also been suggested to be of benefit in case reports [74].

Chronic pelvic pain syndrome (without identified pathology)

The treatment options for CPPS in women has followed a path of empiricism in the absence of a precise pathophysiology to treat. Burkhard *et al.* [75•] proposed that unidentified infection is a potential etiology for CPPS, particularly when there are also symptoms of frequency and urgency, and so suggest that an empirical trial of doxycycline is indicated because 71% of their subjects so treated reported benefit. Open trials of ovarian vein embolization [76], intravaginal electrical stimulation [77•], and acupuncture/electroacupuncture [78] have all had encouraging results, but state-of-the-art care is still undefined.

Sources of pelvic pain in men

Numerous urogenital structures are unique to men, but few result in pelvic pain symptomatology except the prostate. Other pains are more precisely localized to sites in the groin, scrotum, penis or testicles. As such, a majority of studies to date have focused on diseases that had been attributed to the prostate.

Chronic prostatitis/male chronic pelvic pain syndrome

There has been an explosion of interest in chronic pelvic pain disorders in men in the United States as a result of both recognition of the problem and funding put forward by the NIDDK. A chronic prostatitis collaborative research network has been established that developed a tool known as the National Institutes of Health Chronic Prostatitis Symptom Index, which has subsequently been used extensively in studies of this population [79]. The presence of an accepted measurement tool has allowed multiple trials and comparisons to be performed both in conjunction with the chronic prostatitis collaborative research network and outside of it [80•]. An example of one of the descriptive studies that were associated with the Chronic Prostatitis Cohort Study associated with the chronic prostatitis collaborative research network was that of Tripp *et al.* [81•], who identified a poor quality of life in the male CPPS population that correlated with depressive symptoms and pain intensity. Post-ejaculatory pain was identified as one of the factors that was associated with greater pain severity and a poorer prognosis [82•].

Laboratory investigations attempting to identify specific markers or unique characteristics found only in the male CPPS population have generally been disappointing, although differences such as elevations of the cytokines IL-6 and IL-8 in expressed prostatic secretions have been noted [83]. Highly notable findings were those of Lee *et al.* [84], who found that bacteria cultured from prostate biopsies of men with CPPS did not differ from those of healthy controls. Similarly, Nickel *et al.* [85] observed a high incidence of leukocytes and culturable uropathogenic bacteria in samples from 8% of asymptomatic controls. Using polymerase chain reaction assays for specific bacteria, Krieger and Riley [86•] reported that 8% of the prostate biopsies from patients with the diagnosis of male CPPS are positive for uropathogenic bacteria. Interestingly, they also identified that 25% of the CPPS patient samples had evidence of DNA for tetracycline resistance and 77% had evidence of 16S recombinant DNA, suggesting the presence of organisms with those traits.

Recent studies suggest some potential benefit for imaging related to diagnosis using technetium-tagged ciprofloxacin as an agent [87], but the precise value of this imaging modality has yet to be determined. Large prostatic calculi as identified by ultrasonic evaluation appear to be more common in a male CPPS group than in controls [88•]. Subjects were found to be hypersensitive to cutaneous stimuli in sacral dermatomes [89].

The etiology of male CPPS may include bladder-related pathology because 60% of male CPPS patients without any white blood cells in their urine samples had urethrocystoscopic evidence of bladder neck hypertrophy and altered urodynamics [90], and the intravesical administration of potassium solutions produced pain in most patients with the clinical diagnosis of prostatitis (not otherwise specified) [91••]. Yilmaz *et al.* [92•] questioned the utility of the intravesical potassium sensitivity test because in their hands there was no statistically significant difference in the incidence of evoked pain/urgency from subjects with male CPPS and controls.

Many controlled studies have been published relating to the pharmacological treatment of male CPPS. Cheah *et al.* [93•], in a study performed in Malaysian men, observed significant benefit associated with the alpha adrenoceptor antagonist terazosin. Similar results were noted in a multicenter trial in which tamsulosin was utilized [94••]. However, a large multicenter controlled trial of tamsulosin with or without the antibiotic ciprofloxacin failed to observe statistically significant effects, and only observed a trend towards effect in those treated with ciprofloxacin [95••]. In another multicenter trial [96], levofloxacin was similarly without robust effect, and failed to demonstrate statistically significant effects after 6 weeks of treatment. An open trial of antibiotic therapy and nutraceutical administration directed towards nanobacteria demonstrated improvements in

CPPS-related symptoms [97•]. Drugs known to show hormonal effects in the prostate with known utility in the treatment of benign prostatic hypertrophy also demonstrated moderate effects on the symptoms of CPPS in appropriately controlled studies (meparticin [98••]; finasteride [99•,100••]). Anti-inflammatory treatments in the form of the cycloxygenase 2 enzyme inhibitor, rofecoxib, produced statistically greater numbers of subjects in the high-dose treatment group who reported clinically significant improvement [101]. A small trial examining the effects of the leukotriene antagonist zafirlukast failed to observe benefit in the treatment of male CPPS [102•]. Pentosan polysulfate, traditionally used to treat interstitial cystitis, was also employed in the treatment of men with CPPS [103••], and a subgroup within the high-dose group appeared to receive benefit. Nickel *et al.* [104•] also observed that a monotherapy strategy in which sequential trials of all current therapies are performed will only be successful in approximately a third of patients.

Novel therapies that have shown promise in the treatment of CPPS, mainly in open trials, include the use of biofeedback physical therapy [105•], transurethral needle ablation within the prostate [106•], acupuncture [107,108•] and electrostimulation/magnetic stimulation [109,110••,111•].

Conclusion

Increasing evidence has emerged that there are great similarities between differing pain disorders. Hypersensitivity to cutaneous or other somatic stimuli indicating altered central pain processing has been reported in almost every group. Symptom complexes are similar for different disorders, and each group has demonstrated psychological distress and a reduced quality of life. Subsets of each disorder appear to get benefit from modalities giving benefit to a subset of other disorders, with treatments ranging from acupuncture to neuromodulation to systemic drugs. A majority of reports related to novel therapies are uncontrolled but may lead to more controlled studies. As it appears that only subsets of patients respond to particular therapies, it may be necessary to stratify patient groups before testing so that the subgroups responding to therapy may be appropriately identified. Alternatively, as monotherapies have generally proved unsuccessful, at least for large groups of patients, studies may consider following the rules of common clinical practice and combining different agents or modalities of treatment in order to obtain an optimal result.

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