Chronic pelvic pain - traditional and novel therapies: Part II medical therapy

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Summary

Purpose: To describe medical therapeutic options for chronic pelvic pain. Furthermore to describe some new concepts in the etiology of chronic pelvic pain leading to some novel therapies. *Methods:* The benefits and risks of various medical treatments for chronic pelvic pain including central pain, cyclic pain, vulvar pain and bladder pain are discussed. *Results:* Among various conventional therapies the medical therapy with the most benefit with the least risks are low-dose impeded androgens, oral contraceptives, or low dosage progesterone/progestins. *Conclusions:* The various types of pelvic pain may all be different manifestations of a common etiology related to defects in the sympathetic nervous system. Sympathomimetic amine therapy may be the most effective therapy with the least side-effects. However, at the moment this schedule II drug has not been approved for this use and thus must be used off-label.

Key words: Chronic pelvic pain; Deep dyspareunia; Dysmenorrhea; Interstitial cystitis.

Introduction

The introduction in Part I dealing with surgical therapy discussed the various etiologies of chronic pelvic pain with an emphasis on endometriosis. A conclusion reached in Part I was that since various surgical therapies do not provide relief from pain in all women, and even when they do mitigate pain, the relief is far from permanent unless medical therapy is provided after surgery. The one logical approach is that the treating physician should start with medical therapy and use surgery (ranging from conservative laparoscopic ablation to total abdominal hysterectomy and bilateral oophorectomy) for women not getting adequate relief from medical therapy.

Traditionally the laparoscope is used to determine if the pelvic pain problem is related to endometriosis. Thus since ablation of endometriotic implants does at least provide some pain relief, it makes sense if endometriosis is found while performing a diagnostic laparoscopy to laser the endometriosis. However, one should probably resist more risky surgical treatments, e.g., laparoscopic uterosacral nerve ablation or pre-sacral neurectomy.

Medical therapy may be similar whether endometriosis is found or not so my contention is that it is not necessary to diagnose the condition by laparoscopy before initiating medical therapy. A simple non-invasive non-risky ultrasound can help exclude serious ovarian pathology. Measuring the serum CA-125 level during menses or comparing the levels during menses to another time in the cycle can help establish the diagnosis of endometriosis in a non-invasive manner [1-3]. In fact the possibility exists that endometriosis is not the cause of chronic pelvic pain but that endometriotic lesions are more likely to develop in certain chronic pain syndromes related to the mechanisms that are involved in producing the pain.

Standard traditional time honored therapy for endometriosis

Probably the simplest first-line therapy for dysmenorrhea or mittelschmerz is the use of combined estrogen/progestagen oral contraceptives. The theoretical mechanism of action has been considered to be decidualization and subsequent atrophy of endometrial tissue by the progestin component [4]. Since estrogen has been associated with the proliferation of endometriosis it makes sense to use the lower dosage oral contraceptives containing 20 μg of ethinyl estradiol.

The mechanism of relieving dysmenorrhea could also involve the effect of the combined low dose estrogen/progestin oral contraceptive on reducing menstrual flow since heavy bleeding and clots could contribute to dysmenorrhea. By inhibiting follicular development painful events associated with ovulation are inhibited. One of the new concepts is that the progestins may work by inhibiting matrix metalloproteinases [4]. These enzymes may play a role in the growth and implantation of ectopic endometriosis.

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For years the oral contraceptives used had as the progestin 19-nortestosterone derivatives, However, there are data that new generation progestins, e.g., desogestrel can also provide relief of pelvic pain [5]. Though a study using a continuous monophasic oral contraceptive using desogestrel compared favorably to cyproterone acetate, I am not aware of any comparison studies comparing 19-nortestosterone progestins to new generation progestins [5].

Frequently the oral contraceptive will reduce the dysmenorrhea but not enough for adequate satisfaction (or sometimes not at all). In this case one may choose to give the oral contraceptive continuously hoping not to get breakthrough bleeding. There has recently been a new oral contraceptive composed of 20 mcg of ethinyl estradiol and 90 mcg of levonorgestrel approved for continuous use named Lybrel (Wyeth).

Oral progestins

Sometimes instead of the oral contraceptive with estrogen, chronic pelvic pain can be treated by continuous progestins. In fact the so called mini-pill, i.e., 0.5 mg of the 19-nortestosterone derivative norethindrone given continuously is frequently my first choice because of the complete absence of estrogen. In this small dosage it is usually devoid of androgen side-effects. Most of the time eventually amenorrhea develops or the small amount of infrequent breakthrough bleeding is tolerated by the patient.

However, sometimes the amount of breakthrough bleeding is sufficiently annoying or the pain relief inadequate. Sometimes using the same progestin but at a higher dosage, i.e., norethindrone 5 mg once or twice daily will stop the bleeding and improve pain and discomfort. However, at this dosage there may be side-effects of weight gain, acne, or even hirsutism.

Oral impeded androgens

Though many of the progestins in oral contraceptives were 19-nortestosterone derivatives they had progestational properties, i.e., able to induce appropriate secretory changes in the endometrium. Other impeded androgens have been used to treat chronic pelvic pain especially related to endometriosis that do not have a great degree of progesterone effects. The main action causing pain relief is atrophy of endometriotic tissue by creating a pseudomenopause [6]. The most known and used of this class is the 17 alpha-ethinyl/testosterone derivative danazol marketed under the name danocrine (Sanofi-aventis, U.S., LLC).

The recommended dosage of danazol is 600 mg/day [7]. At this dosage androgen side-effects were common. However, similar to the use of the "mini-pill" I have seen benefit in improving chronic pelvic pain even at dosages of 50 mg per day and at this dosage there are little androgen side-effects. There was one study in the late 1990s claiming that the administration of danazol by a novel vaginal ring significantly improved pain from endometriosis, especially the deep infiltrating type but I am not aware that this product was or is about to be commercially marketed [8].

Progestins and impeded androgen administered by intrauterine device

Generally the worst form of contraception to suggest for a woman with dysmenorrhea or dyspareunia is the intrauterine device (IUD) because it will generally cause worse pelvic pain. However, there has been a study suggesting that the off-label use of the levonorgestrel IUD may be effective in relieving the pain of endometriosis [9]. One study found that this IUD improved the degree and speed of the return of pain following laparoscopy vs untreated controls [9]. However, I am not aware of any comparisons to low-dose estrogen oral contraceptive or oral progestins as far as efficacy vs side-effects.

Relatively recently testing an IUD loaded with danazol was found to decrease dysmenorrhea, pelvic pain and dyspareunia associated with endometriosis and this could make it to the commercial market in the near future [10].

Gonadotropin-releasing hormone agonists (GnRHa)

A long acting form of GnRH is created by the substitution of two amino acids into the 10-amino acid decapeptide. Depending on which two amino acids are substituted different GnRHas are developed. Though they initially stimulate luteinizing hormone (LH) and follicle stimulating hormone (FSH) production and release, eventually by ablating GnRH pulsatility, they suppress the gonadotropins and produce amenorrhea and estrogen deficiency. This state will cause atrophy of the endometrium and other endometrial tissue.

Some of these preparations that have been used to treat endometriosis include nafarelin acetate (Synarel, Pfizer) which is used as a nasal spray twice daily and leuprolide acetate which for endometriosis is generally given intramuscularly as a depot form monthly or even every three months.

Though these agents will effectively relieve chronic pelvic pain and the amenorrhea will reduce dysmenorrhea there are generally severe vasomotor symptoms and subsequent problems with vaginal atrophy leading to a different form of dyspareunia and osteoporosis. If a 6-month course of therapy would give long-term relief to the majority of patients then the temporary side effects may be a fair trade. However, long-term follow-up showed that there was a 53% recurrence of pelvic pain within two years of completing GnRHa therapy [11].

A concept was developed of "add-back" therapy, i.e., to use a combination low-dose estrogen-progestin combination that would inhibit the side effects but not obviate the benefits of therapy. Hornstein *et al.* evaluated leuprolide acetate

3.75 mg IM monthly with add-back of either norethindrone acetate 5 mg daily or norethindrone acetate 5 mg plus 0.625 mg of conjugated estrogen or 1.75 mg conjugated estrogen vs placebo [12]. They found that both add back of norethindrone alone or the addition of 0.625 mg conjugated estrogen were equally effective in preventing vasomotor symptoms and bone loss while providing pain relief [12].

Other strategies use the GnRHa analogue for a few months alone until side-effects become unbearable and then add estrogen and progestin. One study used the GnRHa tryptorelin 3.75 mg monthly for four months then added back ethinyl estradiol .03 mg plus an antiprogesterone hormone available in Europe, gestroden 0.75 mg, for eight months and found that to be effective. However, and this is a key point, the pain relief was no better than ethinyl estradiol .03 mg plus gestroden 0.75 mg daily without GnRHa [13]. Thus, in my opinion, since GnRHas are expensive and have serious side-effects when add-back therapy is needed one should try the ethinyl estradiol with gestroden 0.75 mg daily first or just a low-dose oral contraceptive with norethrindone as the progestin (norethindrone is the only progestin approved by the FDA for treatment of endometriosis). In fact, one study found that cyclic use of oral contraceptives was as effective as GnRHa treatment for relief of dyspareunia and chronic pelvic pain and probably, had the continuous oral contraceptive been given, the oral contraceptive would have proven even more effective for dysmenorrhea [11].

Other potential therapies in the near future

Endometriotic tissue seems to have a high level of aromatase activity compared to normal endometrium. Thus one theory as to why postmenopausal women can still have pain from endometriosis may be that the endometriotic tissue can more effectively utilize the small amount of estrogen available to allow the endometriosis tissue to still exist. Thus the use of aromatase inhibitors has been proposed [14, 15]. One study used the aromatase inhibitor letrozole with the addition of norethindrone and claimed significant relief of chronic pelvic pain from endometriosis [16].

Aromatase inhibitors are expensive and also cause side-effects associated with menopause. They are not approved by the FDA for treating endometriosis and thus third party payers will not reimburse for its use for this purpose. Perhaps limited use will be found for postmenopausal women not on estrogen replacement who are still complaining of persistent chronic pelvic pain.

Anti-progestins, e.g., mifepristone and gestrinone have been used for the treatment of endometriosis [4]. Mifepristone is not likely to be commercially developed for this purpose because of its notoriety as an abortifacient. Gestrinone has been tried in Europe and improvement in pain symptoms have been reported [17]. The mechanism of action is not completely clear but it has been suggested that it may cause a progestational withdrawal effect at the endometrial cellular level and could possibly also inhibit ovarian steroidogenesis [4]. Side-effects from blocking estrogen may be similar to GnRHas and aromatase inhibitors and there may also be androgenic side-effects similar to danazol.

A novel concept and therapeutic approach – the use of sympathomimetic amines for the relief of chronic pelvic pain

Though it has been claimed that the laparoscope may be able to identify a cause of chronic pelvic pain such as endometriosis (the main factor), ovarian cysts, pelvic congestion or adhesions 65% of the time, it is not clear that the findings are etiologic or merely more commonly associated with conditions that are causing the pain [18].

If one eliminates cyclic pain from the diagnosis of chronic pelvic pain (which the American College of Obstetrics and Gynecologists has done) and defines chronic pelvic pain as a localized pain of > 6 months duration, one study found endometriosis present in only 28% of the women laparoscoped [19]. Furthermore, as I stated before, its presence does not necessarily mean that it is the cause of the pain.

Interestingly, there are some urologists who believe that up to 85% of women with chronic pelvic pain may have interstitial cystitis [20]. Although one may think that a woman with chronic pelvic pain who also has cyclic pain probably has endometriosis, this is not necessarily true. Some studies have found that interstitial symptoms may worsen in 75% of the cases during the week before the menses [19, 21]. Furthermore 75% of women with interstitial cystitis have exacerbated symptoms following intercourse [22, 23].

Thus if a woman was found to have endometriosis by laparoscopy and she complained of dysmenorrhea beginning a week before menses, dyspareunia, and pain in the lower abdomen radiating to the groin and thighs but also had voiding symptoms, the average gynecologist would conclude that it is not unusual for a woman with endometriosis to also have voiding symptoms especially if there was some bladder involvement with endometriosis. However, if the laparoscopy did not show endometriosis, and if a urologist found ulcers on cystoscopy, or even better demonstrates an abnormal potassium sensitivity test (because cystoscopy is frequently normal in women with interstitial cystitis), then the diagnosis is interstitial cystitis [24-27].

In fact using the potassium sensitivity test one study suggested that interstitial cystitis could be present in one out of 4.5 women and in another study of a larger primary care population it was found in 17.5% of the female population [20, 28].

Actually depending on where is the main focus of the problem, i.e., central or deep pelvic pain, bladder or introitis pain, the symptoms of endometriosis, interstitial cystitis and vulvar vestibulitis overlap. Thus they actually may have a common etiology and be part of one syndrome with a different focal point for the main emphasis of the pain. However careful history will reveal pain in other areas as well. Vulvar pain has been estimated to occur in 20% of women with chronic pelvic pain [19]. Furthermore another study found that 80% of women with vulvovaginitis had interstitial cys-

titis [29]. When women have chronic pelvic pain without evidence of endometriosis or bladder symptoms they are sometimes diagnosed with pelvic congestion. This condition may also be part of this speculation of pelvic disorders.

My contention is this chronic pelvic pain syndrome is actually part of a generalized disorder of the sympathetic nervous system leading to a wide variety of chronic symptoms in women that are generally refractory to conventional therapy [30]. When a person is standing this creates an increase in hydrostatic pressure which would normally cause a shift of fluid from the intravascular to extravascular compartment. However, this is prevented by a signal to the pre-capillary sphincter by the sympathetic nervous system causing it to contract in response to the increase in hydrostatic pressure. In this manner there is an induced decrease in the vascular permeability [31]. Thus women with this condition have a defect in their sympathetic nervous system leading to extra vascular fluid shift.

One of the main symptoms related to the accumulation of extravascular water is fluid retention and accompanying this is weight gain refractory to dieting. When this is the main presenting symptoms the condition has been referred to as idiopathic orthostatic edema [32, 33]. Careful questioning of women with chronic pelvic pain will frequently elicit symptoms of weight gain despite dieting, edema of the face and fingers especially in the morning, edema of the feet, ankles and legs especially as the day progresses. Furthermore, this shift in fluid usually leads to urinary symptoms of nocturia because the fluid becomes mobilized from the extravascular spaces to the intravascular spaces when supine. In contrast decreased urination occurs when the woman is erect for many hours. Once other abnormalities of free water clearance are excluded, e.g., congestive heart failure, cirrhosis, nephrosis and hypothyrodism, the condition of idiopathic orthostatic edema is diagnosed by the demonstration of an abnormal water load test. In the severest form the woman will urinate less than 55% of an ingested water load in four hours when erect but in a milder form the woman will excrete more than 55% but less than 75% of the ingested water load [32, 34]. Sometimes even when the amount of urine excretion exceeds 75% the condition can still be diagnosed by a much greater urinary output supine for four hours vs four hours erect [34].

Other non-pain symptoms associated with this condition include chronic urticaria [35, 36], vasomotor symptoms [37], abdominal distention and bloating especially by the end of the day [30-34], and classic symptoms of hypothyroidism with normal serum thyroid hormone levels [38]. This condition may be associated with non-gastrointestinal or pelvic pain disorders, e.g., severe migraine headaches refractory to standard therapy [39], musculoskeletal pain – including carpal tunnel syndrome, fibromyalgia, and even severe rheumatoid arthritis not amenable to even immunosuppressive therapy [30, 40].

From an abdominal pain standpoint but not pelvic, treatment refractory esophagitis, gastroparesis, and pseudointestinal obstruction may be found [41-43].

From a chronic pelvic pain standpoint vulvovaginitis, interstitial cystitis, and dysmenorrhea and chronic persistent pelvic pain without bladder symptoms may be associated with this syndrome [30, 44, 45].

Evidence to support the concept that these conditions are all part of a generalized disorder of sympathomimetic amines is based on the quick and effective and longlasting improvement in symptoms after treatment with sympathomimetic amines especially dextroamphetamine sulfate [30-45].

The mechanism for pain is not completely clear. One possibility is that edema of these tissues leads to pain. The hypothetical mechanism cannot explain the entire picture because some women gain improvement before the edema is corrected and some pain syndromes improve without an improvement in the edema.

There are many theories to explain the pain from interstitial cystitis. One theory suggests that an increase in epithelial permeability that occurs, possibly by damage to the glycosaminoglycan layer allowing transabsorption of urea and potassium, leads to damage and pain [46].

The defect in capillary permeability was shown by demonstrating that women with idiopathic edema leak radioactively tagged albumin if injected into the circulation when standing compared to women without these symptoms [31]. Within a short interval of two hours the use of dextroamphetamine sulfate will correct the vascular permeability test by allowing the recovery of radioactively labeled albumin in the blood similar to normal women [31]. Thus maybe the sympathomimetic amine also corrects the epithelial defect that may be present in interstitial cystitis [44].

Some urologists favor the concept that most chronic pain, even when there are no bladder symptoms, stems from the bladder related to interstitial cystitis [23, 47]. According to this theory pain impulses emitted by the urinary bladder travel to the spinal cord and due to modulation of these impulses by spinal and cortical signals by the spinal cord "grates" may lead to a rerouting to any location in the pelvis [23, 47].

Sympathetic nerves are the causes of nociceptive and sensory stimuli to the pelvic ganglia especially at T10-T12 [48]. Thus some dysfunction could lead to the interpretation of pain by dorsal horn neurons in the spinal cord [49]. Sympathomimetic amines may correct this abnormal signal.

The dosage of extended release dextroamphetamine sulfate ranges from 10-30 mg daily. Rarely dosages up to 45 mg are needed to suppress the pain. The drug is very well tolerated and side-effects, e.g., insomnia, are generally transient. At these dosages the drug can be suddenly withdrawn without drug dependence or withdrawal side-effects.

Since not all pain syndromes related to this condition are associated with edema the term idiopathic orthostatic cyclic edema does not seem to apply to all cases [31, 32]. Thus for want of a better term I have named this common but frequently undiagnosed condition especially prevalent in women as the sympathetic hyperalgesia and edema syndrome.

Dextroamphatemine sulfate may replace a deficiency of the acetylcholine which is the main sympathetic nervous system neurotransmitter. The deficiency of sympathetic tone (which may be related to demyelinization) leads to increased permeability of the mucosal epithelium leading to absorption of toxins into tissues.

Conclusions

In medicine the drug with the least side-effects weighed against benefit should always be considered when initiating therapy. Since amphetamines are highly effective even when chronic pelvic pain is refractory to a potpourri of other therapies with severe side-effects, I would consider using sympathomimetic amine as first-line therapy especially but not limited to those women showing orthostatic water retention during the water load test. However, because they carry a schedule II label due to potential abuse, and because it would be an off-label use and so not covered by third party providers, I would have to relegate this therapy to women who fail to respond to other benign therapies that even though less likely to work might prove to provide adequate relief. Thus I would likely start the women on low-dose estrogen oral contraceptives or low-dose progestin, e.g., 35 μg of norethindrone only, especially if the main complaint was dysmenorrhea. However, before proceeding to GnRH agonists, high-dose progestins, e.g., 100 mg medroxyprogesterone acetate daily or 5-10 mg norethindrone, or impeded androgens in high dosages, e.g., 600 mg danazol, I would provide the option of off-label use of dextroamphetamine sulfate. I certainly would provide this option before suggesting surgical options. If the main presenting symptom was bladder-related, I might suggest dextroamphetamine sulfate first since oral contraceptives or low-dose progestins are not likely to be effective. Certainly I would give them the option of getting an opinion from a urologist and listen to urologic treatment options and choose which type of treatment with which to initiate therapy.

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