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Conservative treatment of pelvic venous disease

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ABSTRACT

Pelvic venous incompetence (PVI), although usually asymptomatic, may cause pelvic venous disease (PeVD), which may clinically manifest through pelvic symptoms, particularly chronic pelvic pain (CPP). There is no standard approach to manage PeVD and, therefore, the treatment should be individualized based on symptoms and the patient's needs. To date, many treatment methods have been proposed, including conservative treatment, pelvic vein embolization, and reparative surgery. Medical treatment of CPP due to PVI includes non-steroidal anti-inflammatory drugs (NSAIDs), medical suppression of ovarian function, venoprotective agents, vasoconstrictor drugs, and psychotropic agents. The NSAIDs have a short-term efficacy and, due to side effects after longer use, they should be avoided as a long-term solution. Pharmacological suppression of ovarian function may result in CPP relief and may be achieved using medroxyprogesterone acetate, gonadotropin-releasing hormone (GnRH) agonist, long-acting reversible contraceptives, and danazol. They have been proven to be effective in the treatment of pelvic symptoms of PeVD. Venoactive drugs (VADs), particularly micronized purified flavonoid fraction (MPFF) and psychotropic agents, also provide an improvement in CPP related to PVI. A conservative approach represents the first-line treatment modality. It is reasonable to offer such treatment initially, reserving more invasive approaches for resistant cases and patients who present with side effects to the conservative management.

Keywords: Chronic pelvic pain, conservative treatment, hormonal therapy, pelvic venous incompetence.

Pelvic venous incompetence (PVI), although usually asymptomatic, may cause pelvic venous disease (PeVD), which may clinically manifest through pelvic symptoms, particularly chronic pelvic pain (CPP), dysmenorrhea, dyspareunia or prolonged post-coital ache, lower extremity varicose veins (VVs) and/or vulvar VVs, lower-extremity pain and/or swelling, and left-flank pain and/or hematuria.[1]

According to a systematic review by the World Health Organization (WHO), based on 18 studies involving 299,740 women, CPP which is characterized by non-cyclic pain lasting for at least six months, may affect 4 to 43% of women.[2] Pelvic venous incompetence is responsible for 16 to 31% of this disorder. It is very often a comorbidity with other causes of CPP including a wide range of gynecological disorders, particularly endometriosis, pelvic inflammatory disease, adhesions, adenomyosis, and irritable bowel syndrome, interstitial cystitis, musculoskeletal and neurological problems, often with overlapping symptoms in individual patients and, therefore, it is essential to diagnose all these cases, before administering any treatment.[3,4] Among patients presenting with VVs due to PVI, CPP has been reported in less than 10%.[1]

There is no standard approach to manage PeVD and, therefore, the treatment should be individualized based on symptoms and the patient's needs.

The main efforts concern CPP relief. Many treatment methods have been proposed, including conservative treatment, pelvic vein embolization and

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reparative surgery.[1,5] To date, there are no clear guidelines, when conservative approach should be used, and in which cases more invasive treatment is required. The clinical practice shows that 70% of women with CPP due to PVI require only a conservative management.[6] Therefore, it is reasonable to offer a medical treatment initially, reserving more invasive approaches for resistant cases and patients who present with side effects to the conservative management.

Medical treatment of CPP due to PVI includes non-steroidal anti-inflammatory drugs (NSAIDs), medical suppression of ovarian function, venoprotective agents, vasoconstrictor drugs, and psychotropic agents. Psychotherapy may be used in conjunction with medical therapies.

Pharmacological treatment

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are an acceptable, widely described by many authors, first-line treatment of pelvic symptoms of PeVD, particularly CPP and dysmenorrhea, as these agents have a rapid onset of analgesic effect. They may be used to relief the symptoms, while waiting for further investigations or as a more permanent treatment.[6,7]

Unfortunately, NSAIDs have a short-term efficacy and do not affect the cause of the disease. Their administration may be associated with several side effects, including indigestion, gastrointestinal bleeding, inhibition of hematopoiesis and agranulocytosis, particularly after longer use and, thus, they should be avoided as a long-term solution. The duration of such treatment is limited to five to seven days.[6-8]

Pharmacological suppression of ovarian function

The idea of ovarian function suppression in the treatment of pelvic symptoms of PeVD result from the theory of the presence of a hormonal imbalance in patients with PVI.[9] The suggestion that endogenous hormone level implicates the pathophysiology of PeVD issues from the worsening of symptoms during menstruation, an increased prevalence of PeVD in multiparous and premenopausal women, and the positive therapeutic effects of hormonal substitution on PeVD symptoms.[10]

Besides, patients with the pelvic congestion tend to have a larger uterus and a thicker endometrium than healthy women and, in 56% of women, there are cystic changes of ovaries, due to congestion and estrogen overstimulation, combined with insufficient levels of progesterone-like hormones.[11-13] According to Park et al.,[14] polycystic ovaries were found in 40.6% of patients with pelvic congestion and 11.4% of control group, during ultrasound examination. In another study, the mean endometrial thickness was 9.9±1.8 mm in the group with pelvic VVs and was significantly higher (p=0.048) than in the group without pelvic vein dilatation, where the endometrial thickness was measured to be 6.2±2 mm.[15]

Moreover, patients with PVI have significantly higher estradiol levels in blood refluxing to the groin, indicating that hormonal factors play a critical role in the pathophysiology of PeVD.[16]

Estrogen is a potent vasodilator, and its receptors exist on human vascular cells. It causes nitric acid secretion, which relaxes the smooth muscles by stimulating nitric oxide synthase. Nitric oxide not only weaken and dilates the uterine vessels, but also causes pelvic pain.[11]

The main goal of hormonal therapy is to cause a pharmacological suppression of ovarian function and to induce an artificial hypoestrogenic state, which would result in symptoms resolution.

Medroxyprogesterone acetate (MPA)

The MPA is a steroidal progestin, a synthetic agonist of progesterone, which causes an inhibitory effect on estrogen levels through suppression of the hypothalamic-pituitary axis. It is used for contraception, hormonal replacement therapy, treating endometriosis, and chemical castration.

Several studies have shown the long-term benefits of administering MPA at a dose of 30 mg/day for four to six months in achieving optimal hormonal hypoestrogenism and effective reduction of pelvic pain.[9,17] Based on the Farquhar et al.'s[17] randomized-controlled trial (RCT), 73% of women treated with MPA for four months had at least 50% improvement in pain on Visual Analog Scale (VAS), compared to 33% of those treated with placebo. At nine months after the end of therapy, there was no overall significant effect of MPA or psychotherapy alone, although there was an interaction between MPA and psychotherapy, with 71% of the women in this group showing a greater than or equal to 50% reduction in pain score.

The beneficial effect of MPA on pain perception and objectively assessed during venography has been shown in the study by Reginald et al.[18] In this study, 30 mg MPA was administered for six months to suppress ovarian function. In 17 of 22 women who

showed a reduction in the venogram score, the median change in pain score was 75%, compared to only 29% in the five women with no change in the venogram score (p<0.01).

In another RCT performed by Soysal et al.,[9] the treatment with MPA (30 mg/day for 6 months) resulted in a significant improvement in pelvic venography (p=0.001) score as an objective measure, a significant alleviation of pelvic symptoms (p=0.001), a significant improvement of sexual functioning (p=0.001), and a significant reduction of anxiety (p=0.001) and depressive state (p=0.001) at 12-month follow-up, compared to baseline, although the results were inferior to gonadotropin-releasing hormone (GnRH) agonist (goserelin).

An alternative to oral MPA is a subcutaneous form of MPA. Depot MPA (DMPA) is a low-dose subcutaneous form of MPA that is injected at 150 mg/mL, providing efficacy, safety, and immediate onset of action. In a 12-month trial, DMPA depot (150 mg every 3 months) showed an efficacy equivalent to GnRH agonists.[5,12]

The Cochrane review concludes that there is evidence of moderate quality to support MPA as an option for the treatment of CPP; however, the limitations of this therapy are the adverse side effects, particularly weight gain and bloatedness.[19]

Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists have also been used for the treatment of pelvic symptoms of PeVD. Goserelin acetate is a subcutaneous implant of GnRH agonist, which is used to suppress the production of the sex hormones, such as testosterone and estrogen, particularly in the treatment of breast and prostatic cancer, in the management of endometriosis, including pain relief and reduction of endometriotic lesions, and as an endometrial-thinning agent prior to endometrial ablation.

Soysal et al.[9] performed a RCT comparing MPA with goserelin in a group of 47 women with pelvic symptoms of PeVD. The patients received either goserelin acetate (3.6 mg/month for 6 months) or MPA (30 mg/day for 6 months), and the results were compared objectively using pelvic venogram scores and subjectively by symptom resolution, improvement of psychological status, and sexual functioning. At one year after the treatment, goserelin proved to be significantly more effective than MPA in reducing pelvic venography score (p=0.0002), decreasing pelvic symptoms (p=0.00001) and anxiety (p=0.002), improving sexual functioning (p=0.00001), while both agents were similarly effective in reducing the depression subscale scores (p=0.38).

The limitations of GnRH agonists are the side effects, cost, and lack of feasibility of long-term use due to the risk of menopausal symptoms and osteoporosis.

According to the Cochrane review, although the evidence suggests possible benefits of goserelin compared to MPA, the quality of evidence is usually low, and evidence is derived from single-center studies.[19]

Long-acting reversible contraceptives

Long-acting reversible contraceptives (LARCs) includes subdermal contraceptive implants and intrauterine devices (IUDs).

One of the subdermal contraceptive implants which has been proposed in the treatment of pelvic symptoms of PeVD is a non-biodegradable implant consisting of a single-rod containing and releasing etonogestrel, the active metabolite of desogestrel, (ENG, 3-keto-desogestrel), a synthetic steroid, progestogen only, widely used for long-term contraception.[20] The implant provides long-term contraceptive efficacy during the period of three years. It inhibits follicle-stimulating hormone (FSH) activity what causes the ovarian function suppression and a state of hypoestrogenism.[21] After six months, ovarian activity slowly increases and FSH and estradiol levels return to physiological values. In the short term, this blocks ovarian function in almost 100% of cycles, while after 30 months, ovulation occurs in <5% of users. The physiological ovarian activity and the subsequent fertility return within three to four weeks after the implant removal.

The efficacy of subcutaneously implanted ENG in the treatment of pelvic symptoms of PeVD was evaluated objectively and subjectively in RCT by Shokeir et al.[22] At 12-month follow-up, there was a significant reduction in pelvic venography score compared to baseline and control group, as well as a significant improvement in terms of pelvic pain and dysmenorrhea as assessed using either the VAS or Verbal Rating Scale. The total number of days of pain felt from a mean of 15.0 days (6.9) to 6 days (3.4) after 12 months (p<0.001). There was also a significant improvement in the monthly quantified blood loss, compared to pre-treatment. At final evaluation for satisfaction with treatment, 17% women were very satisfied, 66% were satisfied, and

17% were uncertain. All patients were willing to continue treatment with the implant after the end of the study.

The most common adverse effects are irregular periods, weight gain, acne, headache, breast tenderness, emotional lability, and abdominal pain. Despite these side effects, several studies have confirmed that it is a safe, well-accepted contraception method and, therefore, it should be also well-accepted in the treatment of pelvic symptoms of PeVD.[20]

Although ENG implant is a viable option for long-term medical treatment of pelvic symptoms of PeVD, large-scale and long-term studies are necessary to evaluate the effectiveness and recurrence of symptoms after removal.

An alternative may be also 52-mg levonorgestrel-releasing IUD (LNG-IUD). The 24-month follow-up results of a RCT comparing these two products in the treatment of CPP related to endometriosis showed non-inferiority of one over the other in terms of the improvement of CPP, dysmenorrhea, and health-related quality of life.[23] Further studies are needed to validate this method in the treatment of CPP related to PeVD.

An advantage of LARCs is that they are non-estrogenic and, thus, they can be used safely in women with medical conditions such as diabetes, hypertension, systemic lupus erythematosus, and endometrial hyperplasia or in women with a history of solid organ transplantation or current or past venous thromboembolism. These agents have also no negative impact on bone turnover.[20]

Danazol

Danazol is a synthetic steroid with anti-gonadotropic and anti-estrogenic activities that acts as an anterior pituitary suppressant by inhibiting the pituitary output of gonadotropins. It depresses the preovulatory surge in output of FSH and luteinizing hormone (LH), thereby reducing ovarian estrogen production. This leads to a disappearance of nodularity, relief of pain and tenderness, and possibly changes in the menstrual pattern. As a 7-ethinyl-testosterone derivative, it has some androgenic properties.

Danazol at a dose of 600 mg/day has been successfully used in the treatment pelvic pain caused by endometriosis and, owing to anti-estrogenic activity, it has also been proposed in the treatment of pelvic symptoms of PeVD.[7]

Although it relieves the painful symptoms, the use of danazol may be associated with the occurrence of unacceptable side effects, which concern the production of male characteristics, as well as weight gain and acne. However, there is some evidence that women who receive danazol are more satisfied.[24]

Venoactive drugs (VADs)

The use of the VADs, particularly the micronized purified flavonoid fraction (MPFF) in the treatment of pelvic symptoms of PeVD has become more and more popular, as its efficacy has been confirmed in many studies.[25,26]

The main mechanism of action of VADs is the protective and tonic effect on the wall of veins and capillaries, what increases the venous tone. They also improve the capillary permeability and lymph flow, reducing the risk of edema, inhibiting the leukocyte's adhesion to the endothelium of cells and transmigration of leukocytes to venous wall, and improving the rheological properties of blood.

In a cross-over RCT, Simsek et al.[26] assessed the effect of MPFF on CPP related to PVI. The patients either received 500 mg of MPFF twice a day for six months or a vitamin pill for placebo effect, and they were, then, crossed over for another six months. At the end of the third month, the frequency and severity of pelvic symptoms began to decrease with MPFF compared to pretreatment and vitamin arm. The mean scores were significantly lower at the end of six months in this group ($p<0.05$), without any side effects.

In another study, Garilov et al.[25] evaluated the benefit of MPFF in women suffering from CPP associated with isolated dilation of pelvic venous plexus without any deterioration of the vulvar or ovarian veins and with more extended pelvic vein damage, combining both pelvic VVs and gonadal VVs. According to the study, an eight-week MPFF treatment, 1,000 or 2,000 mg per day, yielded CPP relief in women with isolated pelvic VVs. In the long term (up to 60 months), iterative MPFF treatments of an average of three-month courses helped to eliminate CPP in these pelvic VVs patients. In patients with combined pelvic VVs and gonadal VVs, however, MPFF treatment failed to eliminate pelvic pain.

Based on the studies including women with pelvic pain due to PVI, pharmacological enhancement of venous tone with VADs, such as MPFF, may restore pelvic circulation and relieve pelvic symptoms, such as pain and heaviness, in the long-term.[7,25,26]

The rates of adverse effects after MPFF are extremely low (less than 5%). The most common adverse effect is gastric dyspepsia, which usually resolves spontaneously after treatment withdrawal and does not require any specific treatment.[25]

Venoactive drug in post-embolization syndrome (PES) treatment

Percutaneous, endovenous gonadal vein (and internal iliac vein) embolization (EEGV) is the current standard procedure for treating CPP related to PVI, as it is minimally invasive, and its effectiveness has been proven in many studies.[27,28] Despite its high efficacy in relieving pelvic congestion, some researchers have reported persistence or even an increase of pain after the procedure, a frequent complication known as PES.[29-31]

Post-embolization syndrome may result from the development of aseptic inflammation in the venous wall and/or by the patient's hypersensitivity to metals and alloys of which coils are made.[32] The prevalence of allergy to nickel and other nickel-containing alloys in the general population is about 15%.[33] In general, PES lasts up to one month, depending on the patient's characteristics, severity of pelvic vein dilation, and the type of embolization agents used.[32]

The treatment of PES is medical and aims to provide syndrome relief with a rapid rehabilitation of the patient.

Gavrilov et al.[34] analyzed the outcomes of EEGV with coils in 70 women who received or did not receive the treatment with VAD before and after the procedure. The CPP reduction after EEGV was observed in 77.1% of patients. In addition, PES was diagnosed in 18.6% of cases, significantly less often in patients who received VAD before and after EEGV (10.5% *vs.* 28.1%, respectively; p>0.05). The pain in the group with VAD was significantly less severe (6.2±0.4 *vs.* 7.8±0.3 score; respectively; p=0.009) with three times shorter duration (5.0±1.2 *vs.* 16.2±2.7 days; respectively; p=0.003) and, therefore, VADs may be a good option for also patients scheduled for EEGV.[34]

Vasoconstrictor drugs

Dihydroergotamine displays blocking actions at alpha adrenoreceptors, with a direct stimulating effect on the smooth muscle of peripheral blood vessels. Its vasoconstrictor properties are particularly pronounced in veins, compared to arterioles, what causes vein diameter reduction and their tone increase. Dihydroergotamine is used in migraine therapy.

Reginald et al.[35] observed that the intravenous administration of dihydroergotamine (1 mL) in women with pelvic symptoms due to PVI caused a mean reduction of 35% in the diameter of the pelvic veins and a significant alleviation of CPP in 95% of patients within 10 days of treatment. However, the duration of the treatment effect was not specified in the study.

Due to the systemic vasoconstrictor properties, the clinical use of dihydroergotamine requires a special caution due to the narrow therapeutic safety margin, and no therapeutic method has been able to take advantage of the vasoconstrictor properties of this drug. Drug-specific adverse reactions are gastric dyspepsia, headache, dizziness, arrhythmias, induction of myocardial ischemia and/or infarction, cerebral hemorrhage, and stroke.[6]

Psychotropic agents

Prevalence of many psychological disorders are higher among patients with CPP, compared to the general population. Based on the psychological profile of women with CPP, more than 50% have moderate-to-severe anxiety and more than 25% have moderate-to-severe depression.[36]

Drugs with psychoactive action are widely used in the treatment of CPP. The rationale for their use is based on the ability to block nociceptive responses and the reuptake of neurotransmitters by presynaptic nerve terminals, and due to the fact that they decrease the functional activity of beta-adrenergic and serotonin receptors in the brain.[6]

Sator-Katzenschlager et al.[37] conducted a RCT comparing the efficacy and side effects of gabapentin, amitriptyline, and their combination in women with CPP. All patients experienced a significant pain relief during follow-up. However, after 6, 12 and 24 months, pain relief was significantly better in patients receiving gabapentin either alone or in combination with amitriptyline than in patients receiving amitriptyline monotherapy. Side effects were also lower in the gabapentin group than in the other two other groups, and the difference reached statistical significance after three months (p<0.05).

In conclusion, a variety of options for the conservative treatment of pelvic symptoms of PeVD are available, with different modes of action and efficacy. A conservative approach represents the first-line treatment modality, and its use is indicated in women with clinical signs and symptoms of the disease, particularly those with suspected or diagnosed comorbidities that may influence on pelvic symptoms,

patients scheduled for EEGV, and those who are unwilling to undergo EEGV for various reasons. It is reasonable to offer such treatment initially, reserving more invasive approaches for resistant cases and patients who present with side effects to the conservative management.

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