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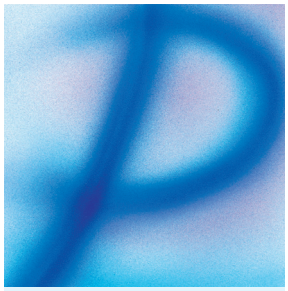

Phlebolymphology

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Aims and Scope

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, and news.

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Contents

Editorial

Dear Readers,

It is estimated that one third of all women will experience chronic pelvic pain in their lifetime. Recent advances show the pain may be due to pelvic congestion syndrome, which is caused by hard-to-detect varicose veins in the pelvis. According to the VEIN-TERM Transatlantic Interdisciplinary Consensus Document, pelvic congestion syndrome is defined as: "chronic symptoms which may include pelvic pain, perineal heaviness, urgency of micturition and post-coital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices".

The aim of the current issue, specially dedicated to the topic of pelvic congestion syndrome, is to collect and review existing data about the prevalence, clinical diagnosis, imaging, and treatment options in pelvic congestion syndrome, with a mind to creating uniform criteria for management of this condition. This issue contains seven articles prepared by seventeen authors from fourteen well-known centers.

The first article describes the prevalence of pelvic congestion syndrome and its main manifestations, such as dyspareunia, chronic pain, atypical varicose veins, and so on. Though epidemiological data don't allow us to make categorical statements, it is obvious that pelvic congestion syndrome is one of the leading causes of chronic pelvic pain in women. In the article, quality of life data from patients with pelvic congestion syndrome are also considered, which confirm the high toll that this medical condition takes on working and social life.

Next, two in-depth articles consider the diagnosis of pelvic congestion syndrome, one of the most difficult steps in its management. Because pelvic congestion syndrome lacks specific symptoms, correct evaluation of all the possible symptoms or manifestations is challenging and extremely important. The results of invasive and noninvasive imaging diagnostic methods (ultrasound, computed tomography angiography, magnetic resonance phlebography, pelvic selective phlebography, etc) define treatment strategy because, on the basis of findings with these methods, it is possible to evaluate the etiology of pelvic congestion syndrome (reflux and/or compression), grade of hemodynamic changes, and the presence of related pathologies of the pelvic area also. A multidisciplinary team approach might be helpful in making a differential diagnosis of pelvic congestion syndrome, as many other diseases of gynecologic, urologic, or neurologic origin may need to be excluded.

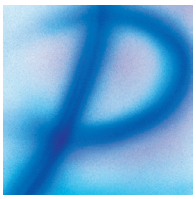
Treatment options for pelvic congestion syndrome are considered in detail in three articles. Of course, it should be noted that, nowadays, less-invasive treatments are the method of choice in the management of pelvic congestion syndrome and surgical methods are used only in cases where endovascular therapy is contraindicated. Authors describe in detail the opportunities for and indications of each endovascular method (embolization and stenting) for different variations of pelvic congestion syndrome. The roles of surgical therapy, sclerotherapy, hormonal and venoactive pharmacotherapy, and psychological approaches in treating pelvic congestion syndrome are also touched on.

Our last article reviews the effectiveness of treatments of pelvic congestion syndrome. On the basis of quite a large body of clinical material, percutaneous endovenous techniques are convincingly shown to be a highly efficient, safe, and cost-effective way of treating pelvic congestion syndrome.

We hope that the current issue gives doctors from different specialties who come across pelvic congestion syndrome in everyday clinical practice the opportunity to better recognize, understand, and treat this debilitating syndrome.

Happy reading.

Pier Luigi ANTIGNANI, Javier LEAL MONEDERO, Santiago ZUBICOA EZPELETA, Zaza LAZARASHVILI



Pelvic congestion syndrome: prevalence and quality of life

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Keywords:

pelvic congestion syndrome; pelvic pain; pelvic varicosities

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Abstract

Pelvic congestion syndrome is an important cause of chronic pelvic pain that develops due to pelvic, but particularly ovarian, vein incompetence. Pelvic pain is one of the frequent reasons for outpatient gynecologic visits. Unfortunately, large and reliable studies on the prevalence of pelvic congestion syndrome do not yet exist; therefore, only indirect data, such as the prevalence of chronic pelvic pain, presence of atypical varicose veins, dyspareunia, etc, can be analyzed. Chronic pelvic pain is often amplified by physical activity and both during and after coitus, and it significantly worsens patients' quality of life and reduces their social activity. A systematic approach and data from large population-based studies are needed to identify the real prevalence and accurately measure the quality of life in patients with pelvic congestion syndrome.

Introduction

In the mid-19th century, Richet observed an association between chronic pelvic pain and the presence of varicose veins in the utero-ovarian plexus; he also described the presence of pelvic varices.[1] In 1949, Taylor first described pelvic venous enlargement as a cause of chronic pelvic pain[2]; this was also shown in 1976 by Hobbs[3] and 1985 by Lechter.[4] In 1984, Beard et al defined pelvic congestion syndrome as a condition characterized by visible congestion of pelvic veins on selective ovarian venography in multiparous, premenopausal women with a history of chronic pelvic pain lasting longer than 6 months.[5] In 2009, pelvic congestion syndrome was described in the VEIN-TERM transatlantic interdisciplinary consensus document as "chronic symptoms, which may include pelvic pain, perineal heaviness, urgency of micturition and postcoital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices."[6]

Prevalence and costs

Pelvic congestion syndrome is an important cause of chronic pelvic pain in women due to pathological venous hemodynamics in ovarian and pelvic veins.

As many as 39% of women have reported experiencing pelvic pain at some time in their life.[7] From 2% to 10% of all gynecological office consultations are for pelvic pain, and nearly 20% of all laparoscopic procedures are performed for chronic pelvic pain. It is estimated that 10 million women suffer from this condition, with approximately 7 million who do not seek treatment.

The economic impact of CPP is astonishing. The annual medical cost for diagnosis and treatment of CPP is estimated to be about $ 1.2 billion. The cost of lost productivity in these patients is estimated to be $ 15 billion annually.[8]

Up to 61% of patients have no explanation for their pain.[8] The worldwide prevalence of chronic pelvic pain has been estimated to vary from 5.7% in Austria to 26.6% in Egypt.[9] It is a common presentation in UK primary care, with 3.8% of women affected annually-a rate comparable with those of asthma (3.7%) and back pain (4.1%).[10]

Noncyclic chronic pelvic pain

According to the first systematic review of the worldwide prevalence of chronic pelvic pain (18 studies; 299 740 women), the prevalence rate of noncyclic pelvic pain ranged from 4.0% to 43.4%.[11] The 3-month prevalence of noncyclic pelvic pain was 15% in women between the ages of 18 and 50 in the USA and 24% in women between the ages of 12 and 70 in the UK.[12,13] The prevalence rates in developing countries in Southeast Asia varied from 5.2% in India and 8.8% in Pakistan to 43.2% in Thailand.[14] Among the causes of chronic pelvic pain, pelvic congestion syndrome accounts for 16% to 31% of all cases, which is second only to endometriosis in prevalence.[9]

Pelvic pain without an apparent cause

In patients with no apparent causes of pelvic pain, ≈30% were shown to have pelvic venous insufficiency,[15] and 10% had ovarian vein dilatation.[16] Pelvic congestion syndrome may develop in up to 60% of women with ovarian vein dilatation.[16] In a study by Soysal et al in 2001, women presenting with chronic pelvic pain were analyzed with a pelvic examination, laparoscopy, ultrasonography, and venography.[17] Of the women screened, 31% had pelvic congestion syndrome as the only abnormality, and 12% had pelvic congestion syndrome plus another pelvic pathology, such as endometriosis, pelvic inflammatory disease, postoperative adhesions, and uterine disease (myoma or adenomyosis).[17] In addition, the incidence increases with the number of pregnancies. This may explain the lower incidence in the USA as the number of pregnancies are lower (1 or 2), whereas, in other countries with higher numbers of pregnancies, the condition is extremely common.[18]

Pelvic varicosities

In 1976, Hobbs examined 1000 women in a vascular clinic and identified a 4% incidence of perivulvar varicosities.[3] Venous clinics that have used pelvic venography or transvaginal or transperineal duplex sonography to evaluate all patients with pelvic pain, Doppler ultrasound evidence of lower limb venous insufficiency, and evidence of pelvic venous origin have shown that 15% to 20% of patients have lower limb varicosities with a partial or complete pelvic origin. However, the percentage of such patients can be as high as 30%.[19-21] Jiang et al reported that pelvic venous insufficiency was the source of non-saphenofemoral reflux in the groin in 6.1% of patients with primary varicose veins.[22] Garcia-Gimeno et al found that reflux from the pelvis or abdominal wall can also occur in 42% of patients with primary varicose veins associated with sapheno-femoral reflux and, in 35% of those, reflux in the anterior accessory great saphenous vein.[23,24]

Depending on the length of the follow-up (5 to 20 years) and the definition of recurrence, between 20% and 80% of patients have recurrent varices after surgery (REVAS), which may result from the development of collateral veins between the pelvis and lower limbs.[25-28] No more than 45% of recurrences occur in the region of the great saphenous vein, suggesting that the cause of pelvic pain is due to reflux in the pelvic veins.[28,29]

Not all women with atypical varicosities have pelvic pain, approximately one-third of those with pelvic congestion syndrome have vulvovaginal varices, and up to 90% may have lower limb varices. Conversely, approximately 5% of women presenting with lower extremity varicose veins will have concurrent pelvic symptoms. It is important to note that pelvic varicosities do not uniformly lead to disabling symptoms. Using CT or MRI examinations, ovarian varicosities have been identified in 38% to 47% of asymptomatic women.[9,30] Often, the real prevalence of pelvic congestion syndrome is unclear and large population-based studies are needed.

Quality of life

Pelvic congestion syndrome is usually diagnosed in women who are younger than 45 and reproductively active (ie, 1 to 2 children); however, evidence-based studies on the quality

of life of patients with pelvic congestion syndrome have not been conducted, and special quality of life instruments have not been developed. Certain factors, such as pain, physical activity, family life, sexual relationship, and work and social life, determine the quality of life of patients with pelvic congestion syndrome.

For pelvic congestion syndrome, patients typically have noncyclic pelvic pain that is usually exacerbated during menstruation and after standing or sitting for long periods. In most cases, pain is assessed using a visual analog scale (VAS). The pretreatment range of pain intensity by VAS in different studies varies between 7.2 and 8.5 points.[9,17,28,31] These values are very high, showing that pelvic pain considerably influences quality of life in patients with pelvic congestion syndrome. The pain is usually localized to the pelvis, but may be present across the whole abdomen and in the lower back. The pain is usually described as a dull ache with intermittent acute exacerbation that is aggravated by physical activity, which primarily affects women's ability to perform their usual daily activities. In addition, the complexity of correctly diagnosing the disease leads to numerous consultations with various specialists (eg, gynecologist, urologist, gastroenterologist, neurologist, and proctologist), and this time-consuming process negatively affects the psycho-emotional status of the patient.

Psychosomatic dysfunction is also inherent for pelvic congestion syndrome. Taylor wrote that "psychiatric disturbances, usually of an emotional character, are a common accompaniment of pelvic congestion."[2] Pelvic congestion syndrome is often accompanied by depression (25% to 50%), anxiety (10% to 20%), and somatic complaints (10% to 20%).[17] Dysmenorrhea, dysuria, and, in particular, dyspareunia are the major factors that influence the sexual relationship between partners. In patients with pelvic congestion syndrome, there is a reduction in the possibilities for both regular work–because sitting or standing for long periods exacerbates the pain–and an active social life.

The assessment of quality of life in patients with pelvic congestion syndrome is very difficult because no disease-specific quality-of-life tools have been developed, and generic quality-of-life tools do not provide sufficient estimates of the quality of life.

Conclusion

Unfortunately, there are no systematic studies to globally understand the prevalence of pelvic congestion syndrome and evaluate the quality of life of these patients. However, data acquired by evaluating individual symptoms, as well as comparing these symptoms with similar syndromes, provide information to predict a high prevalence and poor quality of life. Nevertheless, we need a systematic approach and data from large population studies to identify the real prevalence and accurately measure quality of life in patients with pelvic congestion syndrome.

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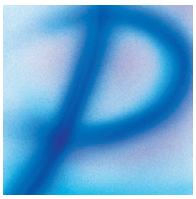

Clinical aspects of pelvic congestion syndrome

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Abstract

The main symptom of pelvic congestion syndrome (PCS) is pelvic pain. Women typically have a dull, throbbing, and achy pain in the vulvar region, which often worsens during or after intercourse, just before the onset of menstruation, and as the day progresses, especially in women who stand or sit for long periods. The cause of PCS is unknown; however, multiple factors, such as venous reflux, venous obstruction, and hormones, are most likely involved. Pelvic pain and refluxing pelvic veins are often present in premenopausal women; however, their presence does not always establish a cause and effect relationship. In patients who have clinical symptoms, signs, and imaging findings compatible with PCS, the diagnosis can be made only after other causes of abdominal and pelvic pain have been excluded. The patient history should include the nature, intensity, pattern, location, duration, and radiation of the pain, as well as any exacerbating and relieving factors. PCS is more often diagnosed in multiparous women younger than 45 years old, possibly because the ovarian veins increase in size during each pregnancy and do not return to normal in women with PCS. The differential diagnoses for pelvic pain are vast, further adding to the complexity of the disorder.

Keywords:

chronic pelvic pain; multiparous; ovarian varices; pelvic congestion syndrome

Introduction

Signs and symptoms

Women with pelvic congestion syndrome (PCS) typically experience a constant dull and aching pain, but the pain is occasionally more acute. The pain is worse at the end of the day, during or after sexual intercourse, just before the onset of menstruation, and after long periods of standing or sitting; relief occurs when the patients lay down.[1-6] Chronic pelvic pain can be debilitating, and it accounts for 10% to 15% of all visits to the gynecologist.[2,6] Hemorrhoids and varicose veins of the perineum, buttocks, or lower extremities may also be present. Ovarian point tenderness during an examination in patients with a history of postcoital pain is sensitive and specific for PCS in 94% and 77% of cases, respectively.[3] Other symptoms and signs include dysmenorrhea, back pain, vaginal discharge, abdominal bloating, mood swings, depression, and fatigue.[4]

Pregnancy

PCS is more often diagnosed in multiparous women younger than 45 years old, possibly because the ovarian veins increase in size during each pregnancy

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and, in women with PCS, the veins do not return to normal. PCS is rarely diagnosed in nulliparous women, and it has not been reported in postmenopausal women. In addition, women with PCS have a larger uterus and a thicker endometrium than women without PCS, and, in 56% of women, there are cystic changes that occur to the ovaries.[3] Often, symptoms do not appear until a woman becomes pregnant, and then they continue after the pregnancy.

Vulvar varices

Vulvar varices occur in about 10% of pregnant women, but typically not during the first pregnancy. Generally, vulvar varices develop during month 5 of the second pregnancy. The risk increases with the number of pregnancies. The incidence of vulvar varices is underestimated because the varices are often asymptomatic; women may be embarrassed to talk about the problem; and doctors are not actively looking for varices when the patient is in a standing position during the physical examination at month 6 of pregnancy or during the first month after delivery. Vulvar varicosities tend to disappear spontaneously after delivery and rarely persist after 1 month.[7] The typical PCS patient may or may not have vulvar varicosities, but they often have varicose veins. The varicosities usually extend along the medial aspect of the medial to posterior upper thigh and along the buttocks *(Figures 1, 2, and 3)*.

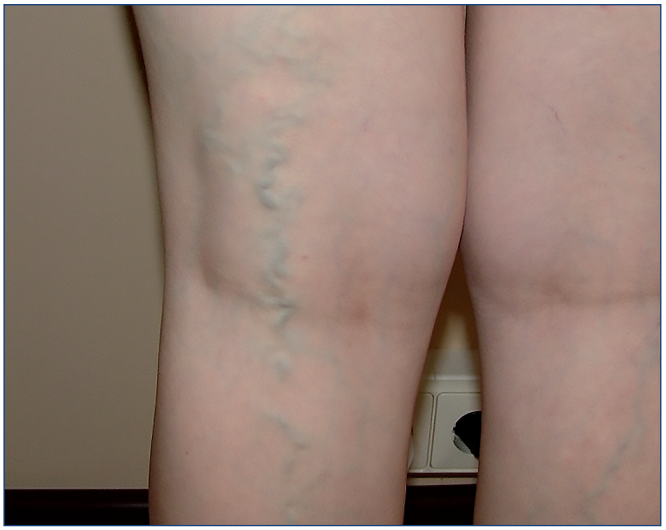

Figure 1. Varicose veins in a patient with pelvic congestion syndrome.

The left leg is presenting more than the right.

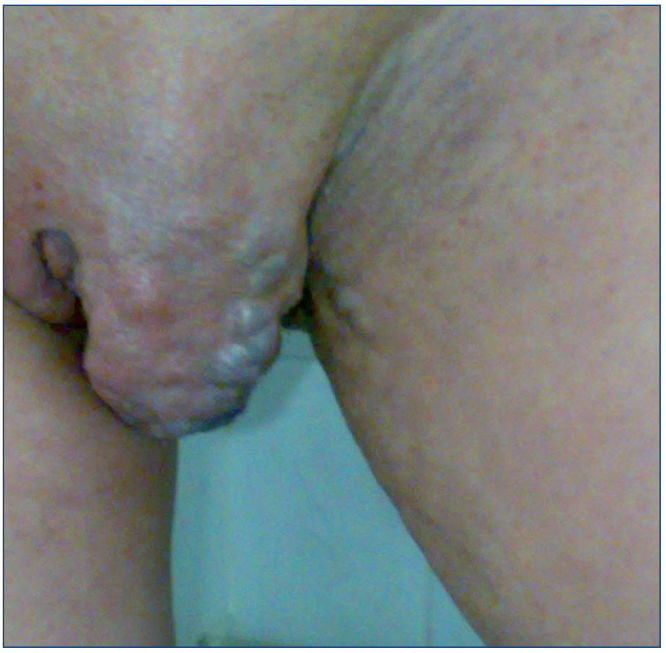

Figure 2. Vulvar varicosities.

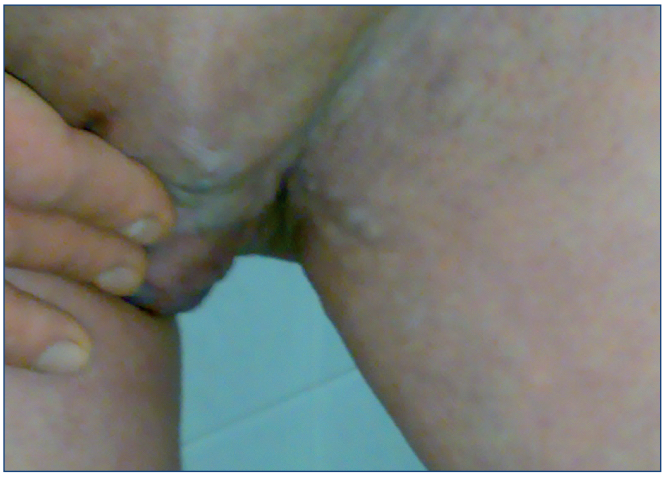

Figure 3. Vulvar varicosities.

Causes of PCS

The cause of PCS is unknown; however, multiple factors, such as venous reflux, venous obstruction, and hormones, are most likely involved. Incompetent and dilated pelvic veins are common, and, according to the literature, 10% of the female population has ovarian varices. Pelvic pain and refluxing pelvic veins are often present in premenopausal women; however, their presence does not always establish a cause and effect relationship.

Patient evaluation

A detailed history and comprehensive examination are of paramount importance. The patient history should include the nature, intensity, pattern, location, duration, and radiation of the pain, as well as any exacerbating and relieving factors. The relationship between the pain and a woman's menstrual cycle should be discussed. Women with depression, personality disorders, and domestic violence have a higher incidence of somatic complaints, and they should seek treatment from a trained mental-health professional. The discussion about patient history should involve a thorough discussion on the patient's sleep patterns, lifestyle (eg, does the pain affect daily activities?), menstrual pattern, dyspareunia, urologic dysfunction, and any other gynecological issues. Irritable bowel syndrome has been reported in 65% to 79% of women with chronic pelvic pain. All previous consultations and diagnostic or therapeutic interventions should be discussed.

The physical examination should evaluate the varicose vein network, which may be present on the perineal, vulval, gluteal, or posterior thigh areas. According to Monedero et al, vulval varicosities develop due to reflux in the left and right ovarian and pudendal-obturator veins in the case of pelvic floor insufficiency; whereas, perineal, gluteal, and posterior thigh varicosities are mostly due to reflux in the internal iliac vein.[8] In addition to an abdominal and pelvic examination, a thorough physical should include an examination of the neurological (evaluating the thoracolumbar spine), cardiovascular, pulmonary, and vascular (evidence of varicosities in the lower pelvis, buttocks, and legs) systems. Further testing should include a complete blood count, metabolic profile, urinalysis, and an endocervical swab for chlamydia.

Differential diagnoses

The main symptom of PCS is pelvic pain, but PCS is not easy to diagnose. Symptoms must be present for at least 6 months before a diagnosis of PCS can be considered.[6] The differential diagnoses for pelvic pain are vast, further adding to the complexity of the disorder. These diagnoses include endometriosis, chronic pelvic inflammatory disease, leiomyoma, adenomyosis, Nutcracker syndrome, diverticulitis, diverticulosis, Meckel's diverticulum, interstitial cystitis, abnormal bladder function, chronic urethritis, fasciitis, nerve entrapment syndrome, hernia, scoliosis, spondylolisthesis, osteitis pubis, somatization, psychosexual dysfunction, and depression. The diagnosis of pelvic congestion syndrome can only be made by excluding other causes of chronic pelvic pain, and managing this complex condition can be a challenge for the primary-care provider.

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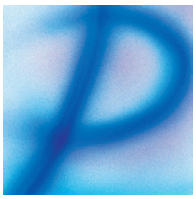

Instrumental diagnosis of pelvic congestion syndrome

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Abstract

Pelvic congestion syndrome (PCS) is a multifactorial medical condition that is characterized by the absence of specific symptoms, and therefore, it needs very precise imaging for an accurate diagnosis. Diagnostic techniques can be noninvasive (duplex ultrasound) or minimally invasive (magnetic resonance, CT, and phlebography). Duplex ultrasound is regarded as a first-line investigation for PCS because it is noninvasive, easily accessible, and inexpensive. This procedure provides essential hemodynamic information, and when combining transvaginal and transabdominal approaches, it could determine the presence of venous dilations, reflux, and compressions. Cross-sectional imaging techniques, such as CT or magnetic resonance scans, are often ordered for abdominal pain, which shows venous varices in the area of the uterus or the pelvis. CT can exclude other pelvic pathologies. In comparison with CT, magnetic resonance venography is superior due to the absence of radiation. Catheter-directed retrograde selective venography or phlebography is the "gold-standard" method for the diagnosis of pelvic venous pathology, in all the variations according to the need. Phlebography confirms the diagnosis and assesses the venous anatomy, especially the collateral venous systems, and it is useful when planning embolization and coil selection. In addition, this procedure is usually performed at the same time as the treatment, with consequent benefits for both patients and physicians. The correct diagnosis of PCS is essential when choosing a treatment option, especially due to the high number of underdiagnosed cases.

Introduction

Pelvic congestion syndrome (PCS) is often underdiagnosed. Therefore, it is necessary to develop a greater awareness among physicians to make a proper diagnosis, to eliminate other pelvic or urological pathologies, and to accelerate treatment *(Figure 1)*. Today, many methods are available to study abdominal pelvic veins by imaging that can give us useful information about potential venous anomalies. These techniques could be separated into noninvasive and minimally invasive investigations, which is dependent on whether catheterization is necessary or not.

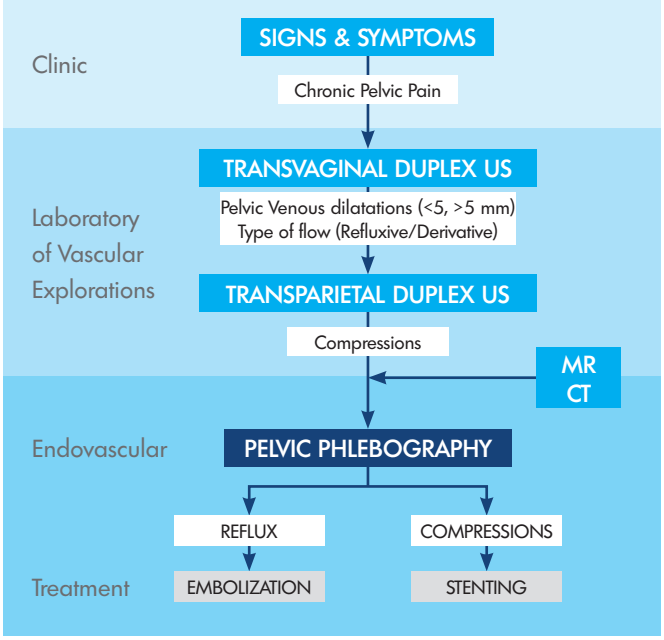

Figure 1. Algorithm for diagnosing pelvic congestion syndrome. Abbreviations: MR, magnetic resonance; CT, computer tomography

Noninvasive diagnostic techniques

A vascular explorations are an essential element in the diagnosis and follow-up of venous disease through noninvasive methods. These noninvasive techniques provide highly reliable and sensitive data on the degree of venous stasis and the permeability and degree of valvular sufficiency in superficial and deep venous systems.[1-3] These techniques can be used to: (i) determine the existence of venous disease, where it is located, and the level of hemodynamic compromise; (ii) diagnose the disease in the early stages in asymptomatic patients of high-risk populations; (iii) identify subclinical venous disorders; and (iv) monitor and evaluate surgery, sclerotherapy, embolization, or medical treatment.

The main instrument is duplex ultrasound. Duplex ultrasound is based on the Doppler effect, which is the change in the frequency of a wave when it bounces off a moving surface, such as blood flow. The device generates and transmits ultrasound waves (not using radiation) through the tissue, that bounce on structures and return to the probe, with a difference in the frequency that is proportional to the speed of blood inside the vessels, providing conversed graphic, acoustic, and colorimetric signals.

Duplex ultrasound scans provide essential hemodynamic information. Duplex ultrasound can determine the direction and speed of blood flow, and it can assess possible obstructions within a vessel. The main problem of ultrasound investigations is that it is completely dependent on the observer; therefore, it is necessary to have specific training to determine all the pelvic venous structures.[4,5] The most appropriate way to investigate pelvic veins by ultrasound is to combine both transvaginal and transabdominal approaches.

Transvaginal duplex ultrasound

Transvaginal duplex ultrasound is performed on female patients in a gynecological position, using a probe that is introduced into the vaginal cavity. It is used to obtain anatomical information and a hemodynamic diagnosis. The sonographic appearance of a normal pelvic venous plexus includes one or two straight tubular structures with a diameter of <5 mm. However, the sonographic appearance of ovarian and pelvic varicoceles is multiple dilated veins (so-called "venous lakes") around the ovary and uterus with a venous Doppler signal of varying amplitude. The presence of circular or linear venous structures with a diameter >5 mm is indicative of pelvic varicosities. The distribution (predominantly anterior or posterior) and side (left, right, or bilateral) should be described. With transvaginal duplex ultrasound, it is also possible to evaluate the presence of reflux, dilatation in gonadal veins, and the existence of uterine-ovarian varicose veins. In addition, a transvaginal duplex ultrasound provides important information for the diagnosis of a possible compression in the iliac vena cava sector or the aortic-mesenteric fork, identifying the presence of centrifugal (reflux), centripetal (derivative), or mixed flow.[5-8]

Transparietal duplex ultrasound

The diagnosis of a compressive syndrome that causes PCS is performed using a transparietal duplex ultrasound, which is essential in morphological studies of the left renal vein and its hemodynamic behavior across the aortic-mesenteric fork. In PCS, transparietal duplex ultrasound can detect pelvic varices and the presence of reflux during a Valsalva maneuver. It can show a possible increase in the flow rate or the reversion of that flow through the left gonadal vein. The flow for an insufficiency pattern is of slow velocity, frequently with dilatation, venous stasis at rest, reflux (lasts more than 1 second), and an increase in velocity with the Valsalva maneuver. It is produced in cases of valvular incompetence of ovarian or internal iliac veins, and it is frequently seen in women with three or more pregnancies. The flow for a derivative pattern is of high velocity at rest (usually ≥5 cm/s), with morphologic dilatation, no visible

reflux, and no reduction in flow velocity with the Valsalva maneuver. It is seen in venous obstruction cases (as occurs in May-Thurner or Nutcracker syndrome and thrombosis or anomalies of the iliac or the cava vein).

To rule out a compressive syndrome of the left renal vein, it is important to measure the ratio of the anteroposterior diameter between the hilar and the aortomesenteric portion of the left renal vein (an anteroposterior ratio >5 is considered abnormal) and the ratio of the peak velocity of the left renal vein between the aortomesenteric and the hilar portion (a velocity ratio >5 is considered significant).

Meanwhile, decreases in flow in the left common iliac vein or reversion through the left internal iliac vein are frequent findings in the compressive May-Thurner syndrome. For detecting left common iliac vein compressive syndrome, it is useful to measure the ratio of the peak velocity between the left common iliac vein (in the site of intersection with the right iliac artery) and the left external iliac vein. A velocity ratio >5 is indicative of significant stenosis. It is also important to visualize the flow direction of the left internal iliac vein (normal or reversed).

Minimally invasive diagnostic techniques

The location and disposition of pelvic veins in the abdominal cavity is very complex. Therefore, noninvasive techniques fail to provide complete anatomical and hemodynamic maps, and it is necessary to resort to other methods.

Computed tomography

Computed tomography (CT) is a minimally invasive method that allows detailed examination of the blood vessels and other adjacent anatomical structures (bones, muscles, organs, etc) without performing a catheterization. CT consists of a multislice helical scanner (64-slice) that provides both continuous high-speed data acquisition in the study area, which is a fast scan that involves a small amount of radiation, and high-quality 3D reconstructions. CT data can be analyzed with specific computer programs, and it can provide a complicated 3D visualization of the relationships between different organs. Therefore, it provides very specific information on the anatomical details, but it has the inconvenience of radiation exposure for the patient. Reflux of the contrast material to the left renal vein generally occurs in the cortical-medullar phase, ie, the arterial phase. When the contrast material is injected into the arterial system and the renal veins (in the arterial phase), simultaneous opacification of the ovarian veins shows ovarian vein reflux.[9] CT is often ordered for abdominal pain, which shows venous varices in the area of uterus or the pelvis. In addition, careful review of the images often shows a large, dilated ovarian vein. On CT, the varicosities are denser than other abdominal veins on postcontrast imaging.

Magnetic resonance angiography

Magnetic resonance angiography is a diagnostic method for obtaining high-quality images without using x-rays. The images are obtained by exposing the patient to a magnetic field with radiofrequency waves that provide both 2D and 3D images of internal organs. Magnetic resonance angiography provides images of blood vessels without contrast administration. It is a minimally invasive technique, and magnetic fields do not cause tissue damage. It is mainly used to study arterial disease, but it is a very useful test to diagnose vascular malformations when it is essential to assess a possible involvement of muscle planes. It is a straightforward and quick (only 20 minutes) procedure. Complete anatomical information is obtained, which can be accurately assessed at different levels and even in 3D, with no x-rays, catheterization, or iodinated contrast. Pelvic varicosities are identified as enlarged tortuous tubular structures in the trajectory of the ovarian veins, around the adnexa, and in the pelvic floor. Pelvic varices can be visualized effectively in 3D magnetic resonance sequences after the administration of intravenous gadolinium, and flow in the pelvic varices appears with high-signal intensity. Furthermore, the renal veins can be assessed for signs of compression (eg, Nutcracker syndrome), and the common and external iliac veins can also be evaluated.[10]

Pelvic selective phlebography

Pelvic selective phlebography is the "gold-standard" technique to confirm a pelvic diagnosis. Phlebography is a radiological technique that involves the opacification of a preselected territory of the venous system for radiographic imaging by injecting intravenous contrast medium.[11,12] The study is performed on a remotely controlled tilt table under fluoroscopic guidance. It is the best procedure for topographic study, and traditionally, it is considered the most reliable method for diagnosis. This study involves inserting a catheter into a vein at the elbow to navigate to the veins of the abdominal and pelvic area, and then dye is injected to obtain high-quality morphological images, even in 3D. This technique can measure pressure gradients, which provides valuable information about the extent of the pelvic venous pathology, and it can provide

morphological information on the veins of the abdomen (ie, iliac veins and the inferior vena cava). It takes place in an ambulatory regime, with no need of hospitalization. The main advantage of this diagnostic procedure is that it is possible to perform the treatment in the same procedure. The main protocol begins with the catheterization of the left renal vein, with simultaneous pressure gradient measurements to investigate for the Nutcracker syndrome. Then, the catheter is moved to the left iliac vein, to do the same for the May-Thurner syndrome. After that, gonadal veins and, finally, internal iliac veins, are investigated. Diagnostic criteria for PCS are the presence of dilated gonadal veins, contrast retention or reflux, congestion of the pelvic venous plexus, or filling of vulvovaginal varices or lower limb leaking points and varicosities.[5,13] The finding of an insufficient gonadal or iliac vein is typically followed by the corresponding treatment.

Ascending phlebography

The ascending phlebography provides an image of the leg veins after contrast dye is injected into a vein in the patient's foot. The patient is placed standing; then nonionic contrast media is manually injected at an estimated dose of 100 cc per limb. An anatomical map of the superficial and deep venous systems is obtained, then the patient is quickly moved into a Trendelenburg position and radiography is performed on the iliac-vena cava sector.

Varicography

Varicography is a modification of the ascending phlebography procedure that is used mainly in patients with recurrent pelvic varices or venous insufficiency. The procedure involves direct catheterization of a varicose area to accurately assess the morphology, extension, drainage channels, etc.

Descending phlebography

The descending venography provides more functional and morphological information on the venous system. It is a complement to the study of the pelvic vascular axes. Descending phlebography is performed by catheterization of the right basilic vein, as a complementary study to selective angiography of the pelvis. It can assess the degree of insufficiency in the deep femoral systems and study recurrent varicose veins of the saphenous-femoral confluences. After exploring and treating the ovarian and hypogastric axes, the catheter is retrogradely moved into the saphenofemoral junction. After injecting contrast during a Valsalva maneuver or standing if a tilt table is available, graphical information is obtained on the valvular competence of the deep venous system, checking for the possible reflux of venous axes. Saphenous systems are also assessed to look for postsurgical varicose recurrence in the saphenofemoral junction, selectively channeling those varicose pedicles for its study.[11,12] Descending phlebography was formerly used for studies on the venous valve system; however, now this valve system is typically assessed by Doppler ultrasound, and descending venography is indicated as a complement pelvic study.

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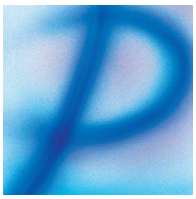

Treatment options for pelvic congestion syndrome

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Abstract

Pelvic congestion syndrome (PCS) and its main symptom, chronic pelvic pain, are caused by an increase in pressure, number, and caliber of intrapelvic venous structures. These structures are veins with a varicose morphology (ie, tortuous and ectatic with a very retarded flow) that are typically caused by inverted flow in the valveless and enlarged gonadal axis and, in some cases, the branches of the internal iliac tributaries. Once a diagnosis is made in symptomatic patients, embolization of the insufficient varicose veins is the preferred treatment. This endovascular procedure is less expensive than surgery, but it is also less invasive, thereby offering a safe, effective, and minimally invasive treatment option that restores patients to normal. The procedure is very successful in blocking the abnormal blood flow in the majority of cases. Embolization is typically performed using mechanical devices, such as coils, in combination with liquid sclerosants. There are different approaches that will be discussed in this article, according to the need of every case. PCS could also derive from a venous compression, such as that observed in the Nutcracker or May-Thurner syndromes. In these cases, besides using embolization, it might be necessary to place a stent to reopen the affected veins to eliminate the pressure that causes venous hypertension and, consequently, PCS symptoms. Other treatments, such as surgical procedures, sclerotherapy, or the use of drugs, can be utilized as an alternative or a complement to endovascular treatments in selected cases, and these alternatives may contribute to symptom relief.

Introduction

Pelvic congestion syndrome (PCS) is defined primarily as nonmenstrual chronic pelvic pain lasting longer than 6 months that is caused by pelvic venous hypertension. Up to 30% of all patients with chronic pelvic pain have no defined cause for their symptoms. Increasingly, PCS is thought to be responsible for the symptoms in many of these patients. Most of the literature related to the diagnosis and treatment of pelvic venous disorders focuses on pelvic pain. As mentioned in prior sections, pelvic venous disorders can also lead to lower extremity and vulvar varicose veins; some authors have reported on the value of treating pelvic venous hypertension to improve these veins and the patient's symptoms.[1] Although these issues should be considered separately when assessing the outcomes of therapy, they are closely related.

Endovascular treatment of pelvic venous disorders

There are multiple options for the treatment of the pelvic venous disorders. For the most part, the treatments are focused on eliminating the venous reflux that is thought to be the most frequent cause of symptoms. Endovascular therapy is the most commonly used approach. It utilizes venography to confirm the diagnosis of a pelvic venous disorder and to define the refluxing pathways, and it provides the possibility of proceeding with the treatment at the same time as the diagnosis. The combined minimally invasive approach is usually performed as an outpatient procedure with a very low rate of morbidity or complications. Endovascular techniques are very efficient not only to treat PCS derived from reflux, but also to treat PCS derived from compressive etiologies, such as the Nutcracker syndrome (left renal compression between the aorta and the superior mesenteric artery), the May-Thurner syndrome (nonthrombotic compression of the common iliac vein by an iliac artery), or other compressions with different etiologies. Compared with surgery, endovascular procedures are less aggressive for the patient.

The pelvic venous syndromes where increased pressure is caused by venous insufficiency can be treated by occlusion of the insufficient axes by embolization. In contrast, venous hypertension derived from compression can be treated using venous stenting, in addition to treating the insufficiencies.

Embolization

As previously stated, embolization has a low rate of morbidity and complications. The first reported case of embolization of uterine-ovarian varices was described by Edwards et al in 1993.[2] Since then, this procedure has frequently been used with positive results in most patients.[3-6] The aim of embolization is to occlude insufficient venous axes as close as possible to the origin of the leak. In pelvic venous disorders, these axes will be the gonadal axes, pelvic varicose veins, and insufficient tributary branches of the internal iliac veins.

The procedure starts with patients in a supine position on the radiological tilt table. One possible approach is to use the right basilic vein at the elbow for venous access. Patient acceptance of this access point is probably higher, the risk of significant arterial or lung injury is low, and immediate ambulation following recovery from any sedation is possible. Alternatively, the internal jugular vein could be used, although patients are more skeptical about the safety and comfort of this access point. However, with ultrasound guidance, the internal jugular vein access point is very safe, and the procedure is well tolerated. In addition, catheter choices, venous catheterization, and catheter exchanges are simpler because the pathway to the pelvic vein is shorter and straighter. When it is necessary to access a retroaortic left renal vein or in cases where catheter access to the gonadal axis is difficult to obtain from the superior cava vein, the femoral vein can be used as an access point.

A renal and left iliac venogram is usually the first step in the evaluation of compressive syndromes, which is done using fluoroscopic-controlled guidance and a multipurpose catheter (80-125 cm, 4-5 F) to measure the pressures between the renal and left iliac veins and the inferior vena cava. Significant left renal and left common iliac vein lesions are identified by either significant compression of the vein, opacification of the collateral veins, or retrograde flow through the gonadal veins. The next step is to cannulate the gonadal and internal iliac veins selectively. The left gonadal vein is a tributary of the left renal vein, and catheterization of this vein is usually done first. The right gonadal vein is a tributary of the inferior vena cava just below the right renal vein, and it is often catheterized next. Contrast medium is injected into the vessel of interest, and the patient (instructed before the procedure) is asked to perform a Valsalva maneuver so that the doctor can check for reflux. Tilting the table into a reverse Trendelenburg position can aid in this evaluation. Retrograde flow toward the pelvis is diagnostic of reflux. Incompetent gonadal veins are generally dilated (>6-8 mm in diameter) and the contrast generally pools in the pelvis after the injection.[7] When an abnormal vein is encountered, treatment is usually performed before evaluating the next vein *(Figure 1)*. The internal iliac veins are subsequently studied using venography. In the internal iliac veins, the Valsalva maneuver will be very helpful to identify insufficiency and to define escape points to the lower limbs. In cases where such reflux is found, it is very important to occlude these vessels to avoid incomplete clinical improvement.

Those axes showing significant caliber increases and retrograde venous flow that fills varicose-like venous veins should be occluded using the same catheter that has already been placed. The embolization material used has varied in the literature, and no evidence-based recommendation can be made about the best approach. Most of the literature has reported using gonadal vein occlusion with mechanical devices, whereas other reports inject a sclerosant into the varicose veins. At this point, no

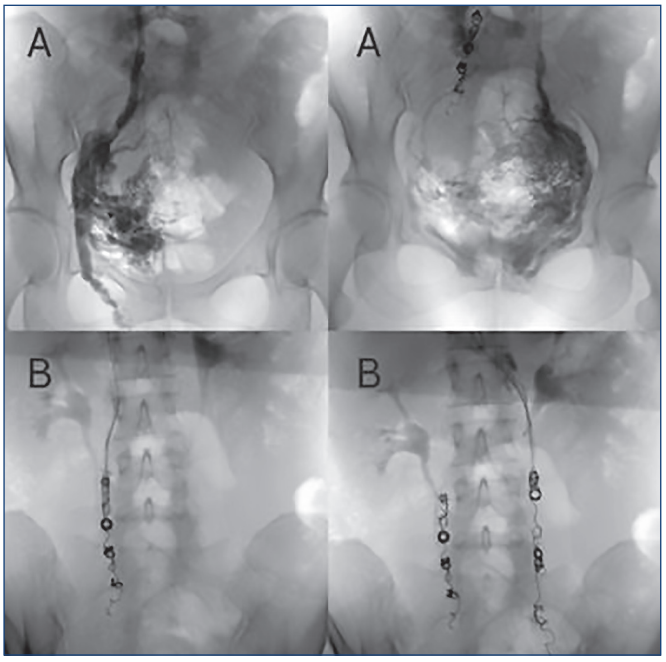

Figure 1. Reflux of gonadal veins can be treated by embolization.

Panels A. *Pelvic selective phlebography showing insufficient gonadal veins in the same patient (**left and right** gonadal veins). When a gonadal vein is refluxive, contrast media flows in a retrograde direction when injected into the proximal portion of the vein and even fills varicose uterine veins.*

Panels B. *Assessment in the same patient after embolization using controlled released (**left and right** gonadal veins). It is important to occlude all insufficient axes by covering the entire vessel to avoid recidivism.*

report on the efficacy of occluding the abnormal pelvic venous plexus alone without occluding the gonadal veins has been reported.

Embolization is typically performed using a "sandwich"-mixed technique, which combines metallic devices with 2% ethoxisclerol foam (prepared according to Tessari's method during the procedure).[8] The treatment is extended proximally to 5 cm from the origin of the gonadal veins off the left renal vein or inferior vena cava, taking care to close all the potential collateral points, either by direct catheterization and embolization or by covering with coils.

As an alternative, the embolization could also begin by injecting a foam or liquid sclerosant (generally sodium tetradecyl sulfate mixed with contrast to result in a 1% to 1.5% concentration) as distally as possible to occlude the pelvic venous plexus using an occlusion balloon just above the true pelvis where the tributaries of the main ovarian vein join. Before sclerosis, the volume of the varicose pelvic venous plexus can be estimated by injecting contrast with the balloon inflated until normal veins start to be opacified. Generally, sclerosis is performed with a volume of sclerosant that is about 75% of the measured volume. After a few coils are placed in the lower part of the ovarian vein, the balloon is deflated and withdrawn a few centimeters, and the sclerosant injection is repeated utilizing a similar sandwich technique until about 5 cm from the termination of the gonadal vein.

To close the gonadal veins, mechanical devices, such as coils of different sizes and plugs, have been used, in combination with different sclerosants. The mechanical devices are safe and efficient, and they are the best option to obtain a complete and durable occlusion. It is desirable to use coils that are 40 to 50 mm in length to cover the entire course of the axis, avoiding the possibility of derivations by collateral systems or anatomic variations. In some cases, segmental mechanical embolization is desired to limit the expense of the coils used. These coils must be of radiopaque materials to allow for fluoroscopic control. The use of controlled-release detachable coils can minimize the potential for migration due to under sizing and allows relocation to occur.

Following gonadal-vein closure, internal iliac veins should be investigated and, if necessary, treated. In the presence of leak points to the lower limbs or connections of internal iliac veins with lower periuterine varicose veins, selective cannulation and embolization with coils and/or sclerosants should be performed.[9] It is important to eliminate all abdominal-pelvic refluxes to minimize the risk of inadequate treatment or recurrence of PCS symptoms. The use of controlled-release detachable coils can be very helpful in those axes to assure that they are placed in the desired location and to avoid migration to a pulmonary artery. Also, it is possible to use an occlusion balloon to find abnormal appearing veins on diagnostic venography and to use the occlusion balloon to sclerose the abnormal components of the pelvic venous plexus as previously described. In men, embolization is used to occlude the left and, less often the right, spermatic vein, vas deferens, and cremasteric vein, thus solving the male varicocele that causes similar symptoms to PCS.

Patients often experience a "postembolization syndrome" after pelvic vein embolization, which is characterized by mild-to-moderate pelvic pain and fever.[1] These symptoms last a few days and can be treated with analgesics. Besides this syndrome, other less common complications have been documented in the literature, such as coil migration to the

pulmonary artery or into the left renal vein. However, the successful recovery of a misplaced coil has been described using an Amplatz loop snare.

Clinical outcomes are monitored after embolization with clinical follow-up visits and a transvaginal Duplex ultrasound at 1, 3, 6, and 12 months postprocedure.

Pelvic leaking point to lower limbs

Pelvic-derived lower extremity varicose veins are found in up to 20% of women with varicose veins.[10,11] The prevalence might be even higher in populations with persistent or recurrent varicose veins after previous treatment.[12] Pelvic-derived lower extremity varicose veins result from pelvic venous hypertension that escapes to the legs through one of four common points. The most common escape point is the perineal or P point, where the internal and external pudendal veins connect in the urogenital triangle. These leaking points can lead to inner thigh and posterior labial varicose veins. The next most common escape point is the inguinal or I point. At this location, pelvic venous plexus–derived reflux passes through the external inguinal ring via a recanalized vein of the round ligament, emerging in the groin medial to the common femoral vein. This can lead to groin and labial varicose veins *(Figure 2)*. Other less commonly discussed escape points include the gluteal points and varicose veins traveling along the sciatic nerve *(Figure 3)*.

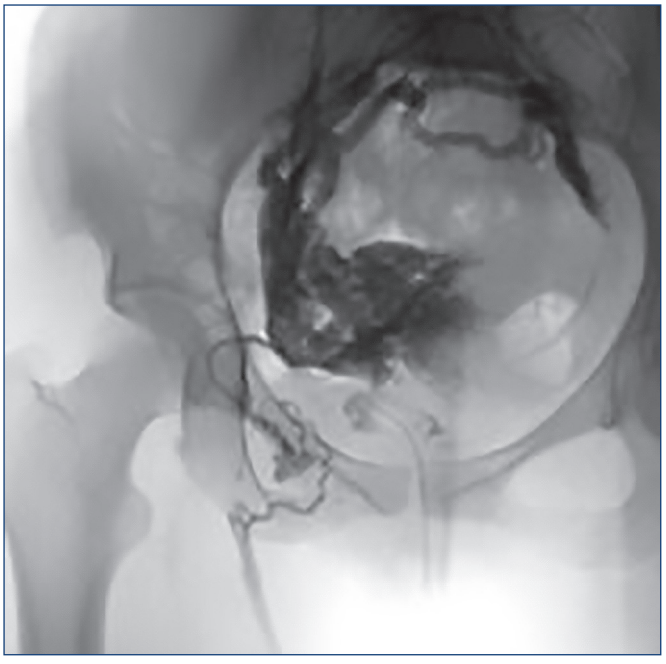

Figure 2. Pelvic leaking point to lower limbs through a round ligament vein.

Pelvic congestion syndrome could affect the lower limbs, which is true in this example of an insufficient right gonadal axis that connects with the uterine-ovarian plexus, making those veins insufficient, and through the right round ligament vein (with a characteristic "C" shape) that connects with the great saphenous vein as a paraostial leak.

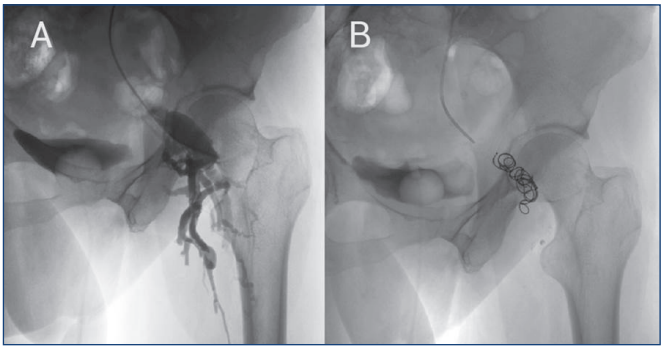

Figure 3. Pelvic leaking point to lower limbs through the gluteal vein.

An insufficiency in the internal iliac axis could leak to lower limbs through the gluteal-ischial axis as is observed in this patient.

***Panel A.** The catheter should be placed as distal as possible in the left internal iliac vein, and when using the Valsalva maneuver, the contrast flows through the left gluteal vein to the left limb through a repermeabilized postaxial axis.*

***Panel B.** After embolization with coils, no contrast is observed in the gluteal axis because the insufficiency has been corrected.*

There are few data on treating pelvic-derived lower extremity varicose veins with pelvic embolization. It is important for physicians to recognize pelvic-derived varicose veins and to consider the value of addressing the pelvic venous hypertension in each case. In patients with both chronic pelvic pain and clinically significant pelvic-derived varicose veins, pelvic embolization is usually done first. Patients with such veins usually require treatment of their leg veins to treat lower extremity symptoms or they require treatment for aesthetic reasons after an embolization is done. In patients with pelvic-derived varicose veins, but no significant vulvar or pelvic symptoms, an alternative approach is to begin by treating the leg veins with contemporary venous treatments in addition to sclerotherapy to treat the pelvic-derived varicose veins from just below the escape points, and then see how the patient responds. Patients with a good clinical response to such treatment may avoid pelvic embolization. If the varicose veins recur early or if the lower extremity symptoms do not resolve after such treatment, embolization can be done afterward.

Sclerotherapy of these veins can be done with visual, transillumination, or ultrasound guidance. With the visual sclerotherapy approach, the amount of sclerosant injected into each vein is empiric and it is generally between 0.5 and 2 mL of an appropriate concentration of 1% polidocanol or 0.5% to 3% sodium tetradecyl sulfate using either liquid or foam. Fluoroscopic-guided sclerotherapy using a mixture of contrast and sclerosant as previously discussed can be done with the advantage of being able to titrate the drug dose to obliterate the connections up to the pelvic venous plexus. Such venographic guidance, analogous to that used to treat venous malformations, allows the operator to identify opacification of normal veins, thereby enhancing safety. The injection can be stopped at that point or continued by manually compressing the connections to a normal vein or manually compressing to direct the sclerosant to the desired targets. Although little evidence has been published to support these approaches; anecdotally, these approaches are effective and durable for patients without significant chronic pelvic pain.

Stenting

Venous compression syndromes could also lead to pelvic venous plexus hypertension and result in PCS. In these cases, placing a stent can treat the compression. A stent is a permanent intravascular device that is placed into the vein using a catheter to reopen narrowed or occluded blood vessels. The stents used in the venous system are usually generally self-expandable and variable regarding the material used and the design of the braids. The stents come in multiple diameters and lengths, and they are selected based on the morphology of the treated vessels and extent of the lesions.

Nonthrombotic compression of the left common iliac vein by the right common iliac artery, often referred to as the May-Thurner syndrome, can also lead to pelvic venous plexus hypertension. Placement of a stent in the left common iliac vein can be performed by a left common femoral vein puncture. The desirable stent would have great radial strength and a high precision placement. Placement of a venographic catheter in the inferior vena cava via a simultaneous right common femoral vein access allows venography to visualize the inferior vena cava confluence, helping to ensure a precise stent placement.

In general, for left iliac vein stenting, the use of self-expandable devices is recommended, in part because balloon-expandable stents are more painful for patients. The most commonly used stent in this location is the self-expanding Wallstent because they are larger than other self-expanding stents. The size used will vary between 16 and 20 mm. A balloon-expandable stent, such as the Palmaz-Genesis series with high radial strength, is utilized in some cases. The recent development of dedicated venous stents with certain desirable properties, such as the Veniti, Sinus Venous, and Zilver stents may change the choice of stents for this lesion as more data on their performance is collected *(Figure 4, Panels A and B)*. The placement of a stent in the iliac vein can eliminate any pressure gradient to venous flow, and it can correct the main PCS symptoms by decreasing the pressure of the collateral flow directed through the pelvic venous plexus. Preliminary data suggest that this treatment of the stenosis may be more important to eliminate pelvic pain than treating concurrent reflux in the gonadal vein if they coexist.[13]

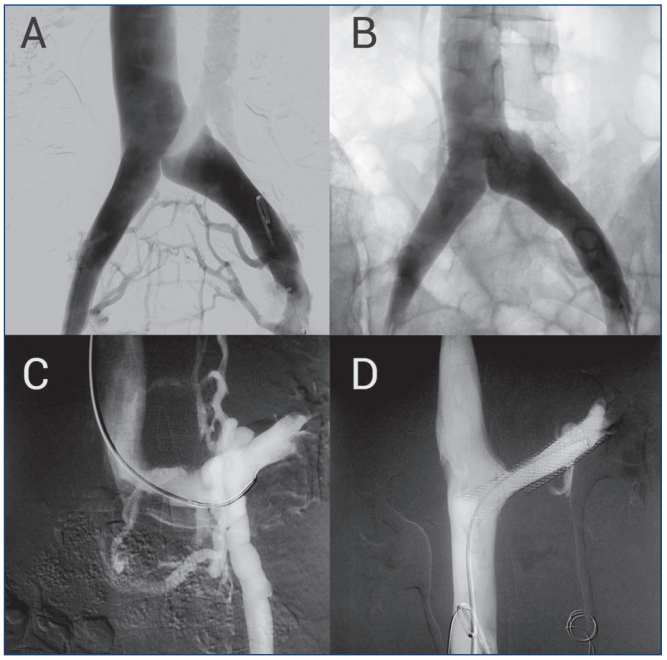

Figure 4. Treating compressive syndromes with stenting.

Panel A. *May-Thurner syndrome or compression of left iliac vein is shown in this pelvic phlebography. The presence of collateral pathways in the uterine and pelvic plexus is responsible for the PCS symptoms.*

Panel B. *After placing a stent, normal blood flow is reestablished, avoiding pathologic collateral systems.*

Panel C. *Nutcracker syndrome or left renal vein compression is shown in the pelvic phlebography. In this case, the pressure increase develops an insufficiency in the left gonadal vein, with the concurrence of an ascending paravertebral collateral system.*

Panel D. *The left renal vein compression is corrected with a stent, which again reestablishes normal blood flow.*

The Nutcracker or mesoaortic syndrome is defined as compression of the left renal vein between the superior mesenteric artery and the aorta (or the aorta and the lumbar spine in the case of a retroaortic left renal vein). Patients with this condition can present with low back or left flank pain and micro- or macrohematuria. Increasingly, it has been recognized that the Nutcracker syndrome can lead to pelvic venous hypertension and chronic pelvic pain by diverting the venous drainage of the left kidney into the pelvis.

Clinical evaluation of patients with chronic pelvic pain and suspected PCS often includes an ultrasound. Duplex ultrasound evaluation of the left renal vein can identify this stenosis by measuring and comparing the diameter and the velocity of flow in the narrow portion and the hilum portion of the vein. Since it is less invasive than the currently available surgical options, it is natural to consider placing a stent in the left renal vein to treat this entity.[4] Since the stent delivery catheter is rigid, thicker, and often shorter than a multipurpose catheter, stenting is performed through the right jugular vein or femoral vein, according to the angle and morphology of the left renal vein. Since the length of the renal vein is short, the risk of stent migration to the pulmonary artery is much higher than in many other locations where venous stents are placed. In addition, the angle of the renal vein and inferior vena cava adds to the challenge of accurately placing a stent. Due to the risk of migration, placing a stent in the left renal vein is not universally accepted using currently available stents. Some experienced physicians who are very skilled with endovascular techniques still think a minimally invasive open surgical approach (in which the left renal vein is transposed lower down on the inferior vena cava with or without a venous cuff, which frees up space between the aorta and superior mesenteric artery) is superior to stenting.

The typical stent choice is a stainless steel self-expandable Wallstent. Proper placement of the stent requires the use of a stent with sufficient caliber as well as avoiding excessive protrusion in the inferior cava vein or into the renal hilum branch veins. If during the release, misplacing is observed, it is possible to resheath the Wallstent device to relocate it properly. The most used stent for the left renal vein is 14 mm in diameter and 40 to 60 mm in length *(Figure 4, Panels C and D)*.

A postprocedure venogram should demonstrate normal flow from the left kidney to the inferior vena cava, without reflux into the gonadal vein or opacification of collateral perirenal veins. Finally, it is desirable to measure pressures before and after the procedure to ensure the normalization of any measured gradient to confirm success, although these pressures are quite low even in patients with severe compression.

Other treatments

Besides the endovascular techniques previously described, there are alternative methods for treating PCS, such as drugs and surgery. These therapies are less frequently used because of their disadvantages compared with embolization, such as a short-term resolution of symptoms or high invasiveness.

For reflux disease, other treatment options include open or laparoscopic surgery to ligate the insufficient veins. However, these procedures are rarely performed because they are more invasive than endovascular embolization procedures, they require a general anesthetic, and the recovery period is longer. Given that surgical ligation can only interrupt the refluxing pathway at a limited number of locations, recurrences may be more common. In many occasions, patients need other complementary procedures, such as sclerotherapy, to correct external leaking points or lower limb varicosities that are derived from PCS. In addition, the use of compression stockings may be desirable to prevent the occurrence or further progression of venous disorders.

Alone, medical treatment is not considered to be valuable for treating PCS. Treatment with medroxyprogesterone acetate or the gonadotropin-releasing hormone analog goserelin acetate may provide short-term relief of symptoms; however, recurrence is common and therefore not typically used for long-term care. Phlebotonics are often used, and they act as modulators of the inflammatory response that is responsible for the pain. However, their value in PCS has not been evaluated.

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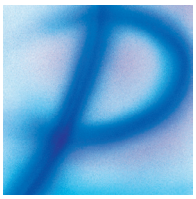

Pelvic congestion syndrome: does one name fit all?

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Abstract

The pelvic congestion syndrome definition includes two not so frequently overlapping scenarios: (i) pelvic venous engorgement with lower abdomen symptomatology; and (ii) lower limb varicose veins fed by pelvic escape points that are generally less prone to develop the abdominal clinical manifestation typical for pelvic congestion syndrome. We retrospectively evaluated 985 female patients (43±11 years old; 23±5kg/m^2 BMI) who visited our offices for lower limb varicose veins of pelvic origin. Second-level imaging was needed for 229 patients. The remaining 756 patients underwent direct echo-guided foam sclerotherapy in proximity of the pelvic escape points. At a mean follow-up of 4.1±1.4 years, 595 patients were successfully treated. Among the successfully treated group, mild lower abdomen heaviness and occasional dyspareunia was reported by 14 and 11 women, respectively, prior to the injection. At the end of the follow up, a significant reduction in the symptomatology was reported for both lower abdomen heaviness and dyspareunia. In traditional pelvic congestion syndrome, an accurate diagnosis protocol eventually ends in an interventional radiology suite. Conversely, in cases of lower limb varicose veins of pelvic origin, the phlebologist can, and in our opinion should, assume a pivotal role both in the diagnostic and therapeutic part.

Keywords:

chronic lower abdomen pain; chronic venous insufficiency; echo-color Doppler; pelvic congestion syndrome; venous reflux

Introduction

As is the case for lower limb symptoms in chronic venous disease (CVD), venous reflux is considered responsible for the clinical presentation of the potentially debilitating pelvic congestion syndrome (PCS), ie, dull aching pain in the lower abdomen, dyspareunia, abdominal and/or pelvic tenderness, dysmenorrhea, lumbosacral neuropathy, urinary frequency, and rectal discomfort.[1] A diagnosis of PCS is usually made after the involvement of several specialists and the exclusion of other pelvic pathologies. Nevertheless, diagnosis and treatment of this disease can become challenging due to multiple and sometimes side crossing interconnections among the ovarian, internal iliac, and femoral veins.[2] Patients with PCS can present with varices of the upper posteromedial thigh, together with varicose veins of the buttocks, perineal, and labial regions. Connections with the great saphenous vein can also feed reflux not involving the saphenofemoral junction, thereby leading an inexperienced sonographer to an incorrect interpretation and therapeutic indication.

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The veins of the pelvis are connected with the lower limb venous system via pudendal, sciatic, gluteal, and perforating veins.[3] Leaking points of the pelvis can feed several patterns of lower limb venous reflux. The denomination of such reflux patterns depends on the anatomical site in which the reflux occurs. *(Figure 1).*[4] The perineal point is located on the perineal membrane where the perineal veins proceed after having received the labial tributaries, thereby connecting the internal and external pudendal systems. The inguinal point is found on the superficial inguinal ring where the veins of the round ligament interconnect with the superficial veins of the anterior abdominal wall and with the vein of the Nuck diverticulum. The obturator point is found inside the obturator canal, and it connects the deep veins of the medial thigh muscles with the internal iliac vein. The superior and inferior gluteal points are found in the gluteal region in association with the sciatic vein and the inferior gluteal veins, respectively.

All pelvic escape points represent leaking points that can actually reduce the venous hypertension of the pelvic region, transferring this overload to the varicose veins of the lower limbs. For this reason, according to our opinion and daily clinical practice, a deeper analysis of PCS is needed. Until now, the PCS definition includes two not so frequently overlapping scenarios: (i) pelvic venous engorgement with lower abdomen symptomatology; and (ii) lower limb varicose veins fed by pelvic escape points that are generally less prone to develop the abdominal clinical manifestation typical for PCS.

In almost 40% of cases, the ovarian and/or internal iliac venous plexus reflux does not extend into the varicose veins of the lower limbs.[5,6] In traditional PCS, the role of the phlebologist is mainly to manage the clinical symptoms and develop a diagnosis protocol that will be carried out by a different specialist. Conversely, in cases of lower limb varicose veins of pelvic origin, the phlebologist can, and in our opinion should, assume a pivotal role both in the diagnostic and therapeutic part.

As such, we in our personal experience (not yet published) retrospectively evaluated 985 female patients (43±11 years old; 23±5kg/m^2 BMI) who visited our offices for

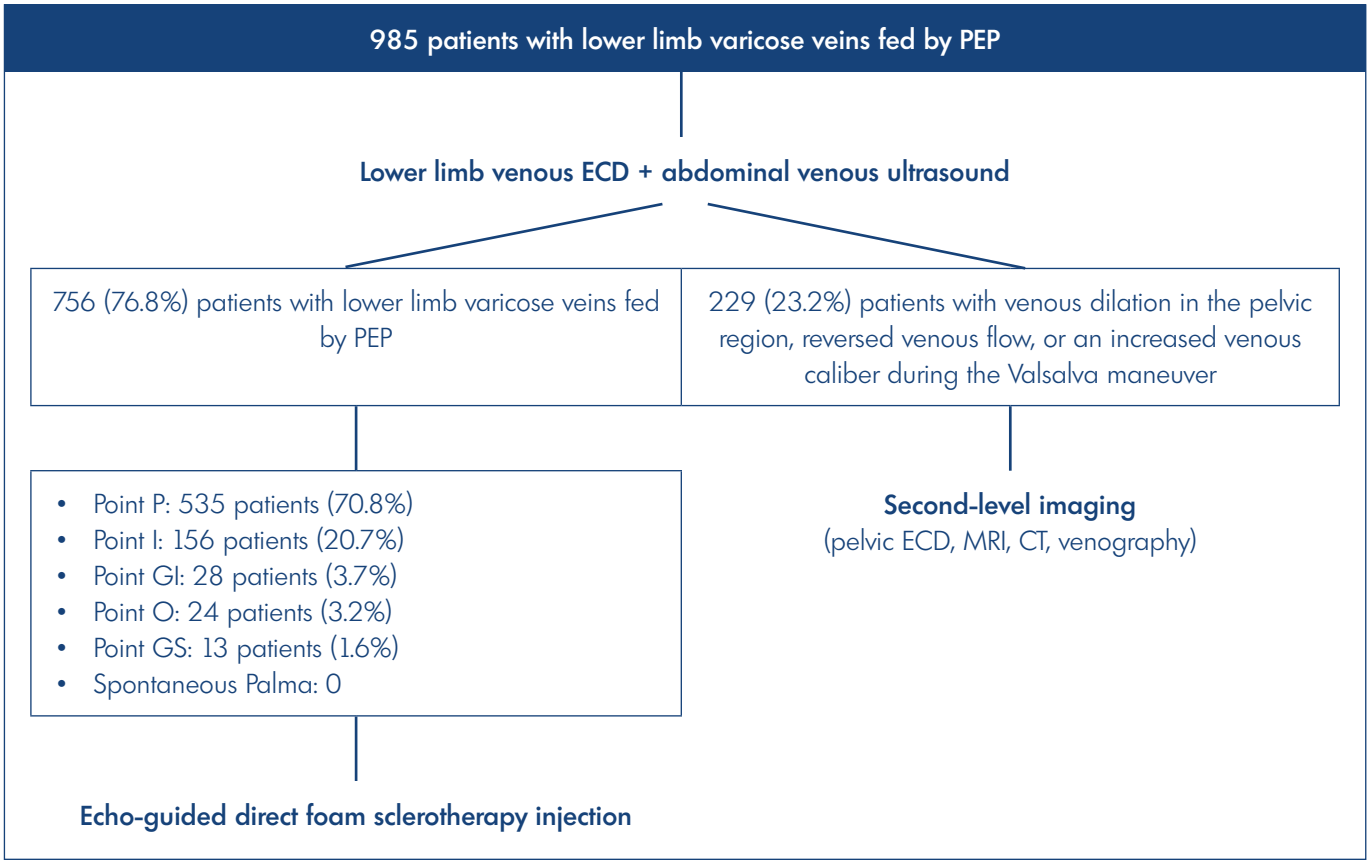


Figure 1. Study population and diagnostic flow chart.

Abbreviations: CT, computed tomography; ECD, echo color Doppler; GI, inferior gluteal point; GS, superior gluteal point; I, inguinal point; MRI, magnetic resonance imaging; O, obturator point; P, perineal point; PEP, pelvic escape point.

lower limb varicose veins of pelvic origin. All the patients underwent an abdominal and a lower limb echo color Doppler (ECD) venous scanning of the lower limbs and the perineal region. Refluxes were evoked both by Valsalva and compression/relaxation maneuvers *(Figure 2)*. The patients were scanned while standing to avoid false negative outcomes. The patient underwent second level diagnostics (pelvic ultrasound, MRI, CT, and venography) when there was an anamnestic suspect, venous dilation in the pelvic region, reversed venous flow, or an increased venous caliber during the Valsalva maneuver. Alternatively, echo-guided foam sclerotherapy injections were directly performed in the proximity of the pelvic escape points. The specific anatomic location of the leaking points are reported together with the diagnostic flow-chart in *Figure 1*.

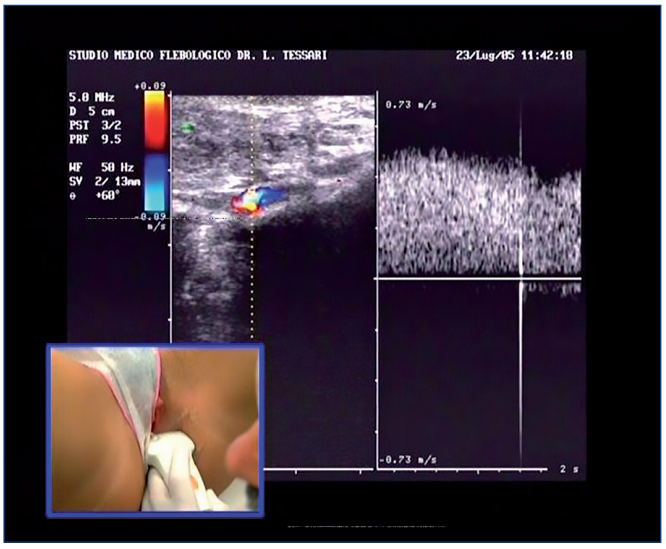


Figure 2. Sonographic evaluation of pelvic reflux evoked by a Valsalva maneuver.

Second-level imaging was done in 229 patients, whereas the remaining 756 patients underwent direct echo-guided foam sclerotherapy in the proximity of the pelvic escape points *(Figure 3)*. All treated patients underwent lower limb and abdominal ECD scanning in the standing position annually after the first injection. At a mean follow-up of 4.1±1.4 years, 595 patients were successfully treated. Reflux was suppressed after 1 injection in 304 patients, 2 injections in 281 patients, and 3 injections in 10 patients *(Figure 4)*. Among the successfully treated group, mild lower abdomen heaviness and occasional dyspareunia was reported by 14 and 11 patients, respectively, prior to the injection. At the end of the follow-up, a significant reduction in the symptomatology was reported for both lower abdomen heaviness and dyspareunia.

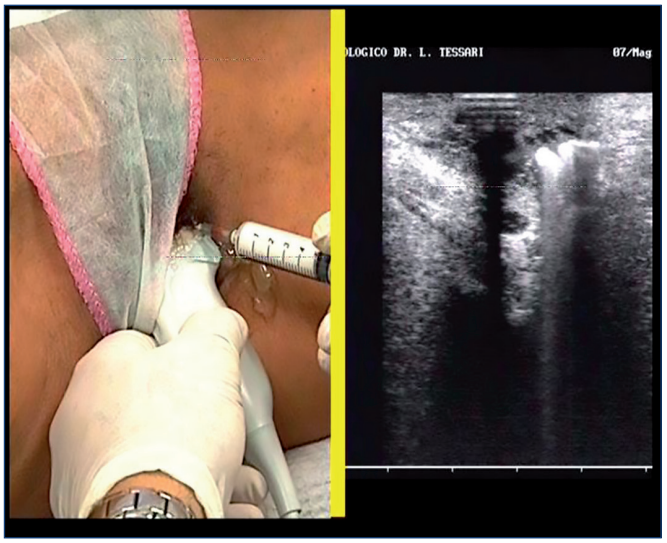


Figure 3. Direct foam sclerotherapy injection and sonographic visualization of the treated venous plexus.

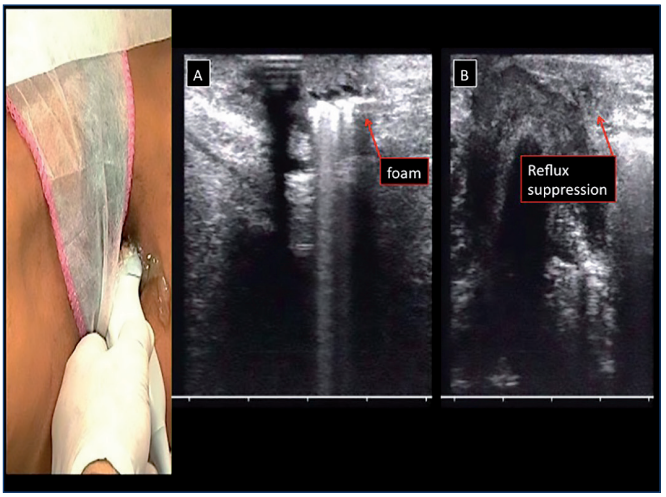


Figure 4.

A. Appearance of hyperechogenic foam after direct foam sclerotherapy injection.

B. Pelvic reflux suppression.

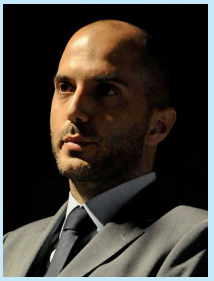
Conclusions

The associated symptomatology with PCS can become extremely debilitating due to chronic lower abdomen pain, dyspareunia, dysmenorrhea, swollen vulva, lumbosacral neuropathy, and urinary urgency.[1-7] An accurate diagnostic protocol requires the involvement of different specialists and diagnostic techniques. Until now, the role of the phlebologist seems to be extremely marginal in this condition, being mainly limited to the assessment and eventual treatment of the associated lower limb varicosities. Nevertheless, in addition to the ovarian and pelvic plexus engorgement,

the PCS definition also includes lower limb varicose veins fed by pelvic escape points. According to our opinion and clinical experience, a clear distinction should be made between PCS and lower limb chronic venous disease of pelvic origin. An anatomical and pathophysiological link exists between the two conditions, but two distinct clinical scenarios characterize these different venous impairments.

On one hand, incompetence of an ovarian/pelvic plexus leads to an engorgement of the lower abdomen drainage system; therefore, leading to the typical symptoms. On the other hand, pelvic escape points feed the reflux that leads to lower limb varicose veins. In an apparent paradox, the leaking points that are feeding the lower limb varices become an escape point for the venous hypertension inside the abdomen. This interpretation provides a possible explanation of the extremely mild pelvic symptomatology in patients affected by varices fed by pelvic escape points. The same reason could explain the increased chronic pelvic pain of PCS patients in cases of lower abdominal venous congestion erroneously treated by ablation of those lower limb varicose veins that were decongesting the pelvic plexus. Moreover, unsatisfactory outcomes of traditional PCS treatments could be related to an incomplete diagnostic work-up.[8]

On this basis, we suggest a careful and consistent evaluation of these different venous impairments, separating the scenario of PCS from the one of Chronic pelvic Venous Disease (CpVD). It is important to pay extreme attention during both the detailed anamnestic interview and the sonographic scanning.



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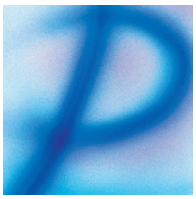

Medical treatment of pelvic congestion syndrome

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Keywords:

chronic pelvic pain; laparoscopy; micronized purified flavonoid fraction; pelvic congestion; pelvis; ultrasonography; varicose veins

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Abstract

Pelvic congestion syndrome (PCS) has no clear etiology and the diagnosis relies on precise investigation techniques. PCS patients present with chronic symptoms in the area of the pelvis, which may have various etiologies; therefore, before any treatment is administered, it is important to exclude other medical conditions that may cause similar symptoms. Treatment options include cognitive behavioral pain management using psychotherapy; medical management that combines pain relief and, if the pain has a cyclical component, hormone suppression; endovenous procedures, such as coil or foam sclerotherapy; and surgery. The choice of treatment depends on symptom severity and the presence of vulvar and lower limb varicose veins. Initially, a medical approach should be offered, reserving surgery for resistant cases and patients who present with side effects to the medical treatment. In the majority of women, medroxyprogesterone acetate (MPA) or goserelin acetate effectively reduced pain and the size of the varicose veins. MPA and micronized purified flavonoid fraction provide short-term improvement, but no data are available on their long-term efficacy. Surgery has progressively been replaced by endovenous procedures with distal embolization of the refluxed veins using a coil and/or a foam sclerosant, and/or by ballooning and stenting the iliac vein compression. Currently, no standard approach is available for the management of PCS; therefore, therapies should be individualized based on symptoms and the patient's needs.

Introduction

Pelvic congestion syndrome (PCS) is described as "chronic symptoms, which may include pelvic pain, perineal heaviness, urgency of micturition, and post-coital pain, caused by ovarian and/or pelvic vein reflux and/or obstruction, and which may be associated with vulvar, perineal, and/or lower extremity varices."[1] PCS is a potential cause of chronic pelvic pain in women of childbearing age.[2,3] Chronic pelvic pain accounts for 10% to 40% of all presentations to obstetrics and gynecology outpatient clinics.[4,5]

Pelvic pain among women is a common condition that may have various causes. The most common causes of pelvic pain not only include PCS, but also endometriosis, pelvic adhesions, atypical menstrual pain, urological problems, spastic colon

syndrome, and psychosomatic disorders.[4] Therefore, the diagnosis of PCS relies on precise investigation techniques. Once the diagnosis is made, the decision to treat PCS is based on the severity of the symptoms and the presence of vulvar and/or lower limb varices.[6]

PCS pathogenesis

PCS is a specific entity that is caused by both dilation of broad ligaments and ovarian plexus veins and an incompetent ovarian vein.[7] It has been reported that PCS occurs in 10% of the general female population and ≈50% of women who have chronic pelvic pain.[4,8] Pain secondary to pelvic congestion increases with fatigue, coitus, and conditions that increase intraabdominal pressure, such as walking, bending, heavy lifting, and prolonged sitting during the premenstrual period.[9] Chronic pelvic pain is generally unilateral.[8,10,11]

Pelvic congestion is diagnosed mostly in multiparous women, while no cases have been reported in postmenopausal women. In multiparous women, PCS is associated with dilated pelvic varices with reduced venous clearance due to retrograde flow in an incompetent ovarian vein. Zehra Gültaply et al found an association between mean number of births and the presence of pelvic varices.[9] During pregnancy, the ovarian vein dilates, permitting a 60-fold increase in blood flow, which is considered to be one of the most important causes of venous insufficiency.[10,12]

The venous congestion stretches over the inner surface of the ovarian vein, distorting both the endothelial and smooth muscle cells. It is postulated that kinking of the ovarian vein leads to venous stasis, flow reversal, and subsequent varicosities.[13] Since the venoconstriction and occlusion of pelvic varicose veins by medical, surgical, or interventional radiological treatment results in an amelioration of the symptoms, PCS is suspected to occur as a result of gonadal dysfunction associated with mechanical factors.[3,14,15] Therefore, this suggests that there is a relationship between PCS and endogenous estrogen levels because estrogen is known to weaken vein walls.[13]

PCS diagnosis

For most interventional radiologists who treat PCS patients, techniques, such as phlebography, magnetic resonance imaging (MRI) or magnetic resonance venography (MRV), and embolotherapy, are at the center of PCS diagnosis and treatment, but laparoscopy in women with chronic pelvic pain remains an alternative method of diagnosis. Chronic pelvic pain is a common clinical entity encountered in gynecology, but it is difficult to establish the true incidence of PCS, given the lack of standard diagnostic criteria and even of clinical suspicion in women with gynecological and urological symptoms. Therefore, the pathology is frequently underdiagnosed. According to the available literature, up to 10% of the general population have ovarian varices and 60% of people with ovarian varices may develop PCS.[5,16]

Since the symptoms are variable, the diagnosis of PCS is difficult. Even after making the diagnosis of pelvic varicosities, the treatment is not always successful and ends with patient dissatisfaction. The severity of symptoms is so variable that a standard therapy protocol is difficult to set up. It is essential that other medical conditions, which may cause similar symptoms, be excluded before any treatment is administered.

PCS treatment options

Treatment options for PCS remained elusive until recently due to controversial diagnostic methods and a poor understanding of its etiology, which ranges from a psychosomatic origin to vascular causes. There is no standard approach to manage PCS; therefore, therapies should be individualized based on symptoms and the patient's needs. Although apparently effective treatments have been devised, it is not clear which could be considered the best option.[17] Various medical and surgical options are available, but a biopsychosocial approach is paramount. A medical approach should be offered initially, reserving surgery for resistant cases and patients who present with side effects to the medical treatment.

Since Topolanski-Sierra first noted an association in the 1950s between chronic pelvic pain and ovarian and pelvic varices,[18] many treatment modalities have been proposed. Medical management with hormone analogs and analgesics, surgical ligation of ovarian veins, hysterectomy with or without bilateral salpingo-oophorectomy and transcatheter embolization have been described in the literature as treatment options for patients with PCS. However, another challenge in the above-mentioned treatments is differentiating patients with endometriosis, which is a common estrogen-dependent disorder in women with chronic pelvic pain, from patients with PCS. This challenge emphasizes the role of enlarged veins in the pathophysiology of pelvic congestion syndrome, which is also estrogen-dependent.

Medical treatment of PCS includes psychotherapy, analgesics, nonsteroidal anti-inflammatory drugs, dihydroergotamine, progestins (contraceptives, hormone replacement therapy, danazol), gonadotropin-releasing hormone (GnRH) agonists, and venoactive drugs.

Psychological approach

Women with PCS are often depressed and anxious, which is partly because they have symptoms for which the cause is often difficult to find. There are also pharmacological and physiological reasons for why they might suffer psychological stress. The venous congestion in PCS causes stretching and shear stress on the inner surface of the ovarian vein, which distorts both the endothelial and the smooth muscle cells. These cells respond by releasing vasodilator substances that include neuropeptide transmitters, such as substance P, neurokinin A, and neurokinin B. These neuropeptide transmitters play a key role in the regulation of emotions and they are an integral part of central nervous system pathways involved in psychological stress.[17]

Psychotropic drugs have been shown to be effective in treating chronic pelvic pain. Gabapentin and amitriptyline were used for this purpose. 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.[19] Side effects were lower in the gabapentin group than in the other two groups, the difference reached statistical significance after 3 months (P<0.05). This study showed that gabapentin alone or in combination with amitriptyline is better than amitriptyline alone in the treatment of female chronic pelvic pain.

Analgesics

Analgesics are a good first-line treatment, but symptoms should not be ignored if it is not completely effective or if pain recurs when treatment is stopped.

Dihydroergotamine

Reginald et al have shown that a 30% reduction in pain can be achieved following the intravenous administration of the selective vasoconstrictor, dihydroergotamine, and that this medication decreased congestion; however, as this effect is only transient, no therapeutic modality has been able to take advantage of this phenomenon.[20] In addition, since dihydroergotamine has systemic vasoconstrictor properties, its clinical application would demand special caution due to the narrow therapeutic margin of safety.[21]

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs are an acceptable first-line treatment because they provide a short-term solution and they may offer some relief while patients await further investigations or a more permanent treatment. However, nonsteroidal anti-inflammatory drugs are not a long-term solution to the patient's problem.[17]

Medical suppression of ovarian function

Medical suppression of ovarian function and hysterectomy with or without bilateral salpingo-oophorectomy have been described as potential alternatives, but are not widely used.[22] Estrogen may have some vasodilatory effects, suggesting that hypoestrogenic states would result in symptom resolution.[17] However, the studies have been small, meaning that firm conclusions cannot be drawn from these studies.

MPA

Medoxyprogesterone acetate (MPA), also known as 17α-hydroxy-6α-methylprogesterone acetate, is a steroidal progestin, a synthetic variant of the steroid hormone progesterone.[23] It is used for contraception, hormone replacement therapy, treating endometriosis, and chemical castration.

MPA has been shown to relieve symptoms in approximately 40% of patients, and a combination of MPA and psychotherapy may be effective in around 60% of patients. However, in one study in which patients were assigned to receive either psychotherapy alone, MPA alone, MPA plus psychotherapy, or placebo, no overall significant effect of MPA or psychotherapy was found, but the combination of MPA and psychotherapy had an effect 9 months after the treatment ended.[24] Weight gain and depression have been reported by patients who do not tolerate MPA.

MPA was also beneficial in 22 PCS patients both subjectively in terms of pain perception and objectively by assessing pelvic congestion using venography. In this study, 30 mg MPA taken for 6 months suppressed ovarian function.[25] In 17 out of the 22 women, pelvic congestion was reduced as shown by venography, and in 16 women, this reduction was associated with an induction of amenorrhea, which suggests that effective ovarian suppression is an important component of successful treatment. In the 17 women who showed a reduction in the venogram score, there was a median change of 75% in the pain score vs 29% in the 5 women with no change in the venogram score (P<0.01).[20,25] Oral MPA, given at a 50-mg daily dosage, was effective in

reducing pain associated with endometriosis at the end of therapy, but the benefit was not sustained.[26]

Subcutaneous form of MPA: DMPA

Depot medroxyprogesterone acetate (DMPA) is a low-dose subcutaneous form of MPA that is injected at 150 mg/mL, and it provides efficacy, safety, and immediate onset of action. In a 12-month trial, DMPA depot (150 mg every 3 months) had effects equivalent to GnRH agonists.[21] DMPA has significant long-term side effects (hypoestrogenic effects, such as hot flashes, bleeding changes, osteoporosis), even if these effects are less than those observed when using leuprolide acetate.[27]

Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone (GnRH) agonists have also been used for the treatment of PCS. An injectable GnRH agonist, also known as goserelin acetate (trade name Zoladex by AstraZeneca), is used to suppress production of the sex hormones testosterone and estrogen, particularly in the treatment of breast and prostate cancer.[28]

In a prospective randomized controlled trial, 47 patients diagnosed with PCS were treated with either goserelin acetate without add-back hormone replacement therapy or MPA for 6 months.[29] Both treatments showed subjective and objective improvements in PCS, a reduction in anxiety levels, and an improvement in sexual satisfaction. However, at a 12-month follow-up after cessation of treatment, a statistical comparison of these agents confirmed a better outcome for goserelin acetate. The main side effects of MPA included weight gain and bloating, whereas the main side effect of GnRH analogs included symptoms of menopause.

Danazol

Danazol, a 17-ethinyl-testosterone derivative, is an antigonadotropic agent for the treatment of pelvic endometriosis[30] that has been used as a medication for chronic pelvic pain associated with endometriosis. At a dose of 600 mg/day, danazol was effective for endometriosis-associated chronic pelvic pain.[31] In 2005, the Chronic Pelvic Pain Working Group considered that hormone treatment for chronic pelvic pain of gynecologic origin, with oral contraceptives, progestins, danazol, and GnRH agonists, should be considered as the first-line treatment for many women, especially those with endometriosis.[32]

Contraceptive implant

Another hormone alternative in women with PCS is Implanon. The synthetic steroid Implanon is a single-rod, nonbiodegradable implant that contains and releases etonogestrel (3-keto-desogestrel), a progestin that is used as a long-term contraceptive method. Implanon blocks follicle stimulating hormone activity, which results in inhibition of ovulation. The implant provides long-term contraceptive efficacy for 3 years. Earlier studies have shown that Implanon suppresses follicular development and steroid production, thereby producing a state of hypoestrogenism.[33,34] Thus, patients with pure PCS due to venous stasis may benefit from this kind of treatment. Several studies have demonstrated that Implanon, as a contraceptive method, was well tolerated, with excellent and reversible contraceptive efficacy.[35] In addition, the use of Implanon in women with PCS obviates the need for repeated treatment where symptoms recur and for additional contraception.[36]

In a prospective open-label study in which 23 consecutive women who were complaining of chronic pelvic pain were randomly assigned to either a subcutaneous insertion of Implanon (12) or no treatment (11), Shokeir et al reported that an improvement in symptoms was observed throughout the 12 months among the Implanon group vs no treatment. The greatest changes in pain, assessed using either the visual analog scale or the verbal rating scale, were between the pretreatment scores and those after 6 months.[37] This 1-year trial showed that Implanon is an effective hormone alternative for long-term treatment of properly selected patients with pure PCS-related pelvic pain.

One of the advantages of Implanon compared with MPA is that the patients regain their fertility more rapidly after discontinuation, often within 1 week.[33,35]

Venoactive drugs

Venoactive drugs, and, more specifically, the micronized purified flavonoid fraction (MPFF*), have been investigated for the treatment of PCS.[38,39] These medications have a protective and tonic effect on the venous and capillary wall, which increases venous tone, improves lymphatic drainage, and reduces capillary hyperpermeability resulting in a reduction in venous stasis. MPFF has been widely studied in the treatment of patients with symptomatic chronic venous disease.[40,41]

Simsek et al conducted a crossover, randomized controlled trial of 20 patients, where randomization was performed in 2 groups of 10 patients.[38] They either received MPFF 500 mg twice a day (treatment group) for 6 months or vitamin pills as placebo (control group) twice a day over

the same period. Treatments were then crossed over for an additional 6 months. Patients were asked to assess their chronic pelvic pain monthly using a 6-point scale (0 for no pain to 6 for intense pain). There was an improvement in pelvic pain scores starting at 2 months in the treatment group compared with the control group, which was significant ($P<0.05$) at the time of the crossover *(Figure 1)*.

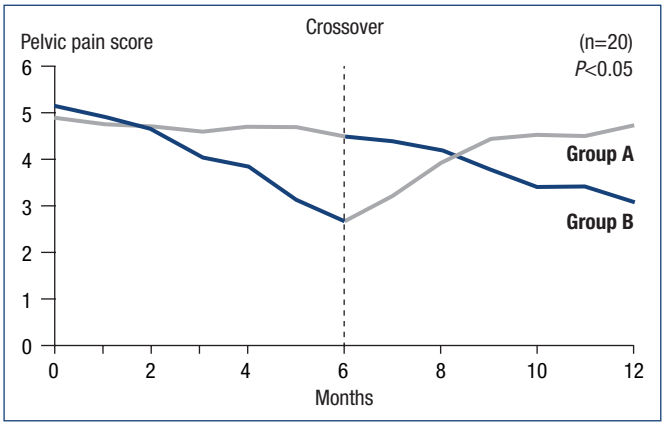

Figure 1. Improvement in pelvic pain scores after a 6-month treatment with MPFF.

Group A. Started with MPFF 500 mg and were then switched to vitamins for placebo effect for 6 to 12 months. Group B. Second arm of the study group received vitamins for 6 months and were then switched to MPFF 500 mg for 6 to 12 months.

Abbreviations: MPFF, micronized purified flavonoid fraction.

Modified from reference 38: Simsek et al. Clin Exp Obstet Gynecol. *2007;34:96-98.*

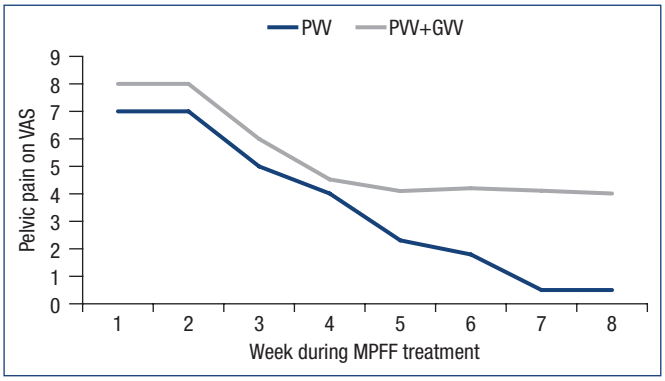

Figure 2. Assessment of pelvic venous pain on a 10-cm visual analog scale.

Patients with pelvic vein dilation in isolated PVV or in PVV + GVV were treated with MPFF for 8 weeks.

Abbreviations: GVV, gonadal varicose veins; MPFF, micronized purified flavonoid fraction; PVV, pelvic varicose veins; VAS, visual analog scale.

Modified from reference 39: Gavrilov et al. Angiol Sosud Khir. *2012;18(1):71-75.*

This study showed a statistically significant improvement in pelvic pain scores in both groups, without any side effects.

In a trial by Gavrilov et al, 85 women suffering from chronic pelvic pain associated with pelvic varicose veins in isolation (PVV group) or with both pelvic and gonadal varices (PVV+GVV group), MPFF at 1000 mg a day for 8 weeks was more efficient in PVV patients with isolated dilatation of uterine and parametrial veins than in the PVV+GVV group.[39] A continuous decrease in pain was reported by the PVV patients up to week 8 of treatment, and symptoms completely disappeared at 14 weeks. The clinical effect persisted for a long time (6 to 9 months) with a stabilization of the disease course *(Figure 2)*. In addition, pelvic venous congestion declined, as shown by emission computed tomography, reflecting a restoration of the pelvic circulation in this group *(Figure 3)*. There was no additional pain reduction in the PVV+GVV group.

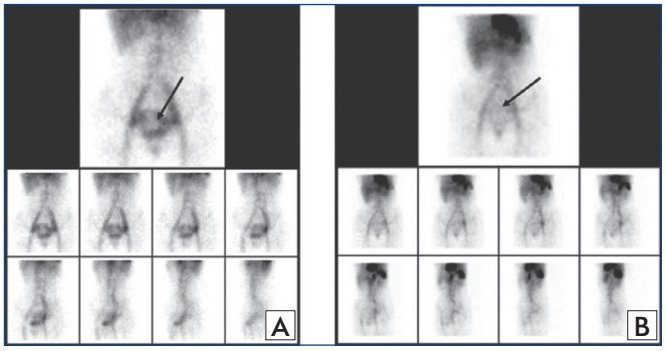

Figure 3. ECT assessment of pelvic veins before and after MPFF treatment.

ECT of the pelvic veins at baseline (Panel A) and after an 8-week MPFF treatment (Panel B) in a patient with pelvic vein dilation in isolated PVV. Deposit of labeled erythrocytes in the uterine venous plexus is indicated by the arrows.

Abbreviations: ECT, emission computed tomography; MPFF, micronized purified flavonoid fraction; PVV, pelvic varicose veins.

From reference 39: Gavrilov et al. Angiol Sosud Khir. *2012;18(1):71-75.*

Based on these two studies on women with PCS, initial pharmacologic enhancement of venous tone with venoactive drugs, such as MPFF, may restore pelvic circulation and relieve pelvic symptoms, such as pain and heaviness, in the long-term.

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Long-term effectiveness of medical treatments

The above-mentioned studies have shown that medical management of PCS can prove to be beneficial for women; however, there is insufficient evidence regarding their long-term effectiveness in controlling their debilitating symptoms. Specifically, GnRH agonists may be used for 6 months without add-back hormone replacement therapy or up to 2 years with add-back hormone replacement therapy to reduce the risk of osteoporosis. Therefore, the use of progestins should be further evaluated as a long-term treatment option for PCS, taking into account that bone density is slightly reduced during usage. The reduction in bone density appears to be reversible and it is probably of minor clinical significance in women in their second and third decade; however, there are some concerns about the reversibility of bone mineral density reduction in women in their early and later reproductive years.

Long-term benefits of MPA and/or GnRH agonists have been demonstrated previously.[20,24,33,35] In fact, long-term therapy with progestins appears to be more favorable than with GnRH analogs. The limitations of GnRH agonists were side effects, costs, and the inability to use them for a long-term course due to the risk of menopausal symptoms and osteoporosis. Of the progestins cited above, Implanon seems to offer good results in pelvic pain alleviation with tolerable side effects in selected patients with symptomatic and pure PCS. Overall, nearly 80% of the women were satisfied after 3 months of treatment. Implanon probably is an option for long-term medical treatment and it should be more extensively evaluated for this indication in comparison with other medical treatments.

Patients who are refractory to medical therapy may then be considered for ligation, embolization, or sclerotherapy of the ovarian veins. However, randomized clinical trials have not yet distinguished or identified a top choice between existing invasive techniques.

A look into the future

The conclusion drawn by the Chronic Pelvic Pain Working Group in 2005 could be applied to the medical treatment of PCS in the future, particularly to women with PCS who are complaining of chronic pelvic pain:

...in the future, a woman with chronic pelvic pain will be recognized as having a condition that requires rehabilitation and not solely acute care management. She will be managed by a team of individuals who are aware of the principles of multidisciplinary care, including a physiotherapist, a psychologist, a primary care physician, and a gynecologist.

Such an approach will be funded by the local hospital or regional health authority on the basis of its effectiveness and cost efficiency. Emphasis will be placed on achieving higher function in life with some pain rather than cure. The management of directed therapy will be based on treatments that have been subjected to clinical trial. There will be a permanent record of the findings at any previous laparoscopy that can be shared and compared over time. Health personnel involved in the patient's management will have been trained in the specific areas of this disease management.[32]

Finally, a multidisciplinary approach to diagnosis and care is currently recommended.[32]

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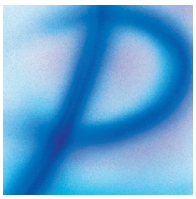

Effectiveness of treatment for pelvic congestion syndrome

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Abstract

Pelvic congestion syndrome accounts for approximately 16% to 31% of patients suffering from chronic pelvic pain, and it is the second most frequent cause of pelvic pain after endometriosis. It is a poorly understood disease, and various treatments have been suggested in the past. Hormonal treatment, which suppresses ovarian function, demonstrated varying results. Hysterectomy with salpingo-oophorectomy used to be the second option for treatment, though efficacy of this treatment is disputable. In the more recent past, endovascular techniques for abolishing pelvic vein incompetence have been introduced with varying success. Additionally, deep venous obstruction caused by left renal vein entrapment or iliac vein compression has been identified as an important component of pelvic pain. Percutaneous endovenous techniques seem to be the best alternative as the initial treatment option. Several studies have also suggested that psychosocial factors weigh heavily on treatment outcomes, so concurrent psychotherapy may be useful when treating these patients. Future research should focus on reproducibility of treatment procedures, and randomized controlled trials should determine whether treatment of pelvic venous obstruction or incompetence is useful in relieving chronic pelvic pain. Then, properly designed studies should identify the importance of treating obstruction before incompetence. Finally, the additive effect of psychotherapy should be investigated.

Introduction

Pelvic congestion syndrome (PCS) is a poorly understood syndrome that is characterized by a vague chronic pelvic pain that persists for at least 6 months.[1-3] Pain is usually described as being dull or a feeling of heaviness on one side of the abdomen; however, more localized complaints have also been described.[1,4,5] Complaints usually exacerbate around the menses or during and after coitus. As with venous incompetence, complaints are typically aggravated at the end of the day and during long periods of standing or walking, and can improve when assuming the supine position.[1,5] The role of pregnancy is unclear in this syndrome, although complaints usually increase.[1] Furthermore, PCS is associated with the presence of varicosities in the vulvovaginal, gluteal, peritoneal, and lower limb areas.[1,3]

The prevalence and incidence of PCS are unclear due to the broad differential diagnosis of pelvic pain, the unclear pathophysiology of PCS, and the difficulties

in diagnosing PCS as the cause of pelvic complaints. PCS is the leading cause of chronic pelvic pain after endometriosis, and it is estimated to account for 16% to 31% of cases.[5] Due to the poorly understood etiology, treatment of PCS can be a difficult venture. This paper will evaluate the effectiveness of possible treatment options for PCS.

Hormonal treatment

Since PCS usually occurs in premenopausal women and it is usually not found in postmenopausal women, it is hypothesized that hormones play a role in PCS.[1,6] Therefore, hormone therapy that suppresses ovarian activity could be useful when treating PCS.[7] Studies included in a recent systematic review diagnosed PCS using the criteria of Beard et al,[8] while other causes of pelvic pain were excluded through laparoscopy and ultrasound. The Beard criteria focus on three venography findings, appointing a score of 1 to 3 to each finding: the maximum diameter of the ovarian vein (1-4 mm, 5-8 mm, or >8 mm), time of disappearance of contrast medium from end of injection (0 s, 20 s, or 40 s), and congestion of the ovarian plexus (normal, moderate, or extensive).[9]

Some studies have shown a beneficial effect of medroxyprogesterone (MPA) on a visual analog scale for pain.[10-12] Reginald et al[11] did not have a control group; however, after treating patients for 6 months with 30 mg MPA daily, patients with a venogram score reduction showed a 75% decrease in the visual analog scale score compared with only 29% in those without a venogram score change (P<0.01). Farquhar et al[10] performed a well-executed randomized controlled trial with 4 groups: 4 months of 50 mg MPA, MPA + psychotherapy (6 sessions), placebo, and placebo + psychotherapy. At the end of treatment, 73% of the patients in the MPA groups showed a ≥50% reduction in visual analog scale scores compared with 33% in the two placebo groups (P<0.001). However, 9 months after cessation of treatment, the effect decreased for MPA and psychotherapy when administered alone, while the effect in the placebo group did not change. The combination of MPA and psychotherapy showed that 71% of patients had a ≥50% reduction in visual analog scale scores 9 months after cessation of therapy (P<0.05).

Although MPA appears to have a positive effect on pelvic pain in PCS, gonadotropin-releasing hormone (GnRH) agonists seem to have a superior effect. Soysal et al[12] compared 30 mg MPA daily with a 3.6 mg goserelin acetate injection every month for 6 months. The final evaluation occurred 12 months after cessation of treatment, and the data demonstrated a 7.7±1.8 and 4.7±1.4 decrease in pelvic pain with goserelin acetate vs MPA, respectively (P=0.00001) on a modified version of the Biberoglu and Behrman[13] pelvic symptom score (score varying from 0 to 12). However, no information on other treatments during the cessation period was given. A case series of 21 patients did not yield successful results with a combination of goserelin acetate, estradiol valerate, and MPA,[14] yet in this small group, 2 patients underwent a hysterectomy or oophorectomy and 5 patients discontinued treatment during the study. Shokeir et al[15] compared a subcutaneous etonogestrel insert with no treatment for 12 months, and the data showed a significant difference in visual analog scale scores between treatment and no treatment (7.7 before vs 2.4 after Implanon, 7.9 before vs 7.6 after with controls; P<0.05). However, patients were not blinded to the treatment.

Hysterectomy and salpingo-oophorectomy

Oophorectomy used to be considered for those who did not respond to hormone treatment. Oophorectomy was combined with hysterectomy to prevent withdrawal bleeding due to hormone replacement therapy.[6] Beard et al[6] reported a case series in which bilateral oophorectomy with hysterectomy, usually after failed hormone treatment, demonstrated a change from a median visual analog scale score of 10 to a median visual analog scale score of 0 at 1-year follow-up (P<0.001). A total of 24 patients (66.7%) demonstrated full relief from pain, 11 (30.6%) experienced significant improvement, and 1 (2.7%) showed only a slight improvement. Chung et al[16] were not able to reproduce this effect in a randomized controlled trial comparing ovarian vein embolization with hysterectomy and unilateral salpingo-oophorectomy (USO) or bilateral salpingo-oophorectomy (BSO). Hysterectomy with USO did not show a significant reduction in visual analog scale scores (7.8 to 5.6; P>0.05), while hysterectomy with BSO showed a change in visual analog scale scores from 7.7 to 4.6 (unclear whether statistically significant). This randomized controlled trial had some limitations because the inclusion process was not transparent, patients were not blinded to the treatment and the randomization procedure was not described.

Elimination of ovarian vein and internal iliac vein incompetence

Congestion of blood in the pelvis can result from incompetent ovarian veins or internal iliac veins *(Figure 1)*. Data on surgical correction of ovarian vein incompetence through ligation is scant.[17,18] Focus had quickly been

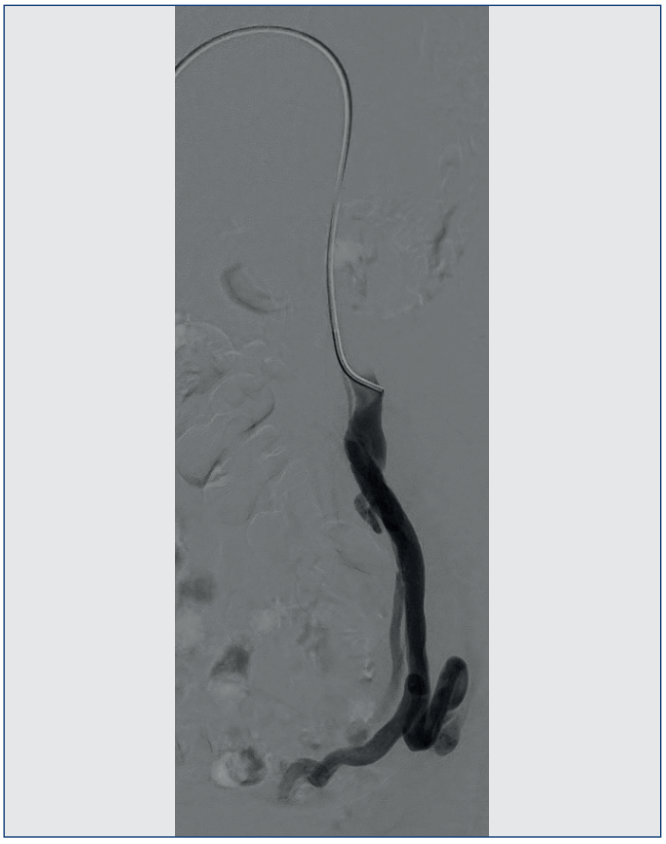

Figure 1. Venogram of an incompetent left ovarian vein with pelvic collateralization.

diverted to less invasive, percutaneous techniques. The study of Chung et al,[16] which was discussed in the previous section, demonstrated a significant decrease in the visual analog scale scores for ovarian vein embolization (7.8 to 3.2; *P*<0.05) with better results than hysterectomy with USO or BSO. Furthermore, data suggest that a psychological effect is important in PCS, as fewer patients demonstrated improvement in complaints in the group who scored high on stress scoring questionnaires based on the revised social readjustment rating scale (40.2% for severe stress scores vs 56.4% for moderate and 61.5% for low). It should be noted that the group of patients with high-stress levels was small (7 severe vs 18 moderate and 27 low).

Other studies have not used a control group and these studies have been composed of prospective or retrospective case series.[1,4,7,16,19-36] The definition of PCS varied in these studies and was not always clearly stated. While some studies used visual analog scale scores for outcome measurement, many studies only used general clinical improvement when reporting outcomes with complete relief of symptoms varying from 50% to 100%.[20,21,27,29,31-33,35]

Laborda et al[28] described the largest population (n=202) with the longest follow-up (5 years). The mean visual analog scale score was 7.34±0.7 before the procedure compared with 0.78±1.2 at the 5-year follow-up (*P*<0.0001). However, only 179 patients reached the 5-year follow-up, and inclusion criteria for PCS were based on symptoms and venography results, as opposed to the criteria established by Beard et al.[8] Also, patients were initially referred with lower limb varicosities, after which PCS symptoms were identified by a questionnaire. The left ovarian vein was coiled in all patients, while the right ovarian vein was coiled in 193 (95.5%), the left internal iliac vein in 184 (91.1%), and the right internal iliac vein in 149 (73.8%) patients. It should be noted that the average time for clinical improvement was 13.5±1.9 months in those with severe pain (8-10) compared with 9.1±1.1 months in those with moderate pain (5-7; *P*=0.001). Initial follow-up visits were planned for 1, 3, 6, and 12 months after treatment.

Nasser et al investigated patients who suffered from chronic pelvic pain for at least 6 months, in combination with tenderness at the ovarian point during a physical examination.[30] If venography demonstrated an incompetent ovarian vein or internal iliac vein, coiling was performed. It was not stated how many patients were analyzed, although 113 women underwent embolization, of which 13 were lost to follow-up and therefore excluded from analysis. Embolization was done in 100% of left ovarian veins, 72% of right ovarian veins, 80% of left internal iliac veins, and 46% of right internal iliac veins. Mean visual analog scale scores decreased from 7.34±0.07 to 0.47±0.05 at the 1-year follow-up (*P*<0.001). All patients reported significant improvement with 53 patients having no pelvic pain and 47 patients showing a reduction in pain. Multivariate analysis showed that complaints of urinary urgency and lower limb symptoms yielded an odds ratio of 5.9 (95% CI, 1.5-23.4) and 5.3 (95% CI, 1.4-20.4), respectively, for the risk of incomplete resolution of symptoms. Furthermore, a larger diameter of the right ovarian vein was associated with a higher chance of complete clinical success.

Kim et al[26] studied the effect of coil embolization with an injection of a foam sclerosant of the ovarian veins and internal iliac veins in 127 patients; 20 patients and 106 patients underwent unilateral or bilateral ovarian vein embolization, respectively, with 1 patient in whom the treatment was unknown. At 4 to 6 weeks after the initial procedure, venography was performed to test and treat for internal iliac vein incompetence (n=108 patients). Mean follow-up was 45±18 months, with complete follow-up for

97 patients. Visual analog scale scores were significantly reduced for overall pain (7.6±1.8 before and 2.9±2.8 after; *P*<0.000001), dyspareunia (3.3±3.7 before and 1.5±2.7 after; *P*<0.000001), and menstrual pain (4.9±4.2 before and 2.2±3.1 after; *P*<0.000001). A total of 80 patients demonstrated clinical improvement; 64 significant, 11 moderate, and 5 mild. A recurrence rate of 5% was observed. Patient selection for this study was not uniform, and it was initially based on clinical suspicion of PCS. The proportion of patients who were nulliparous was very high compared with other studies (63%), although no significant differences in treatment effects were observed between multiparous and nulliparous patients.

Other smaller studies have shown comparable results.[19,22,24,25,34,36] Complications were infrequent and not severe.[5] A retrospective analysis by van der Vleuten et al[35] showed that 9 out of 21 patients underwent more than one embolization with Histoacryl. After the second embolization, 4 still showed no improvement and 1 worsened; 2 patients underwent a third and fourth embolization without any success. However, it should be noted that the results were obtained through a retrospective questionnaire at a mean of 18.1 months (range, 4-60 months) after the first intervention.

Treatment of the Nutcracker syndrome

Nutcracker syndrome is caused by a compression of the left renal vein due to entrapment between the superior mesenteric artery and the aorta *(Figure 2)*.[37] Hartung et al[38] treated 5 patients with PCS, who also demonstrated left renal vein entrapment. All patients received a self-expanding metallic stent (Wallstent, Boston Scientific-Schneider, Minneapolis, MN) in their left renal vein. The first patient experienced migration of a 20x60 mm stent into the retrohepatic inferior vena cava. The stent was snared and pulled back, although it adopted a transversal position in the inferior vena cava, just cephalad to the left renal vein, and was left in place. A new 16 mm stent was successfully placed and all subsequent patients immediately received a 16 mm stent. Patients received low-molecular-weight heparin for 15 days and clopidogrel for at least 6 months, and 2 patients received this treatment in combination with a vitamin K antagonist.

At 1 month after stenting, all patients experienced an improvement in their symptoms. Duplex examination showed a patent stent and relief of ovarian vein incompetence in the 3 patients who had not had a previous ovarian vein embolization. A total of 2 patients were asymptomatic at

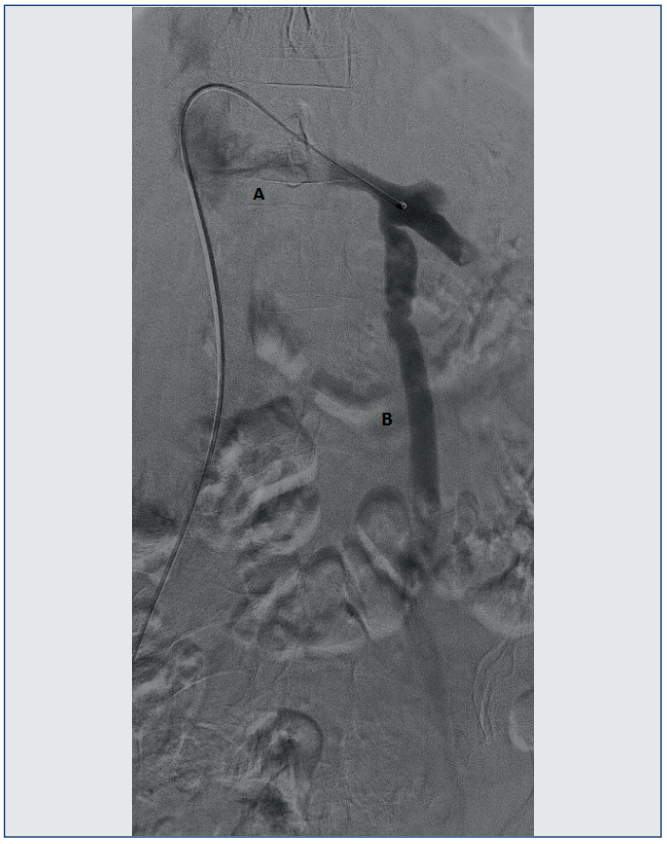

Figure 2. Venogram of the left renal vein.

***A.** Lack of contrast filling in the renal vein due to the Nutcracker phenomenon. **B.** Incompetent left ovarian vein as a collateral route for left renal outflow.*

4.2 and 26.5 months postintervention, 1 patient developed a different kind of pelvic pain at 15 months postintervention and underwent hysterectomy for endometriosis; no such signs were found during the laparoscopy before stenting, and 2 patients had symptom recurrence at 3 and 4 months postintervention. Duplex ultrasound and computed tomography showed minor stent migration to the right side of the inferior vena cava, which caused left renal vein compression to recur. No further complications were encountered. The indication for stenting was not uniform. It was based on symptomology, exclusion of other pathologies (all underwent laparoscopy), and confirmation of a Nutcracker syndrome on duplex ultrasound, computed tomography, and venography. Patients suffered from either PCS symptoms or flank pain, the latter occurring in 2 patients who initially reported with PCS complaints at 2 and 3 months after ovarian vein embolization.

A study by d'Archambeau et al[23] described the presence of left renal vein compression in 40 out of 48 patients who underwent ovarian vein embolization; 12 patients

showed extrinsic impression with retrograde filling of paralumbar veins and/or ovarian veins, 16 patients showed compression with filling of side branches including the ovarian vein and reflux toward the renal hilum, and 12 patients showed a total compression of the renal vein. Compared with other studies on ovarian vein embolization, a similar treatment effect was observed by only treating the ovarian vein incompetence and not treating the renal vein compression. However, both pre- and postprocedural visual analog scale scores were retrospectively obtained through a questionnaire at an unknown point after the procedure had already taken place. Moreover, no tests assessing kidney function were performed. Therefore, no information is available on kidney damage due to impaired renal outflow.

Nutcracker syndrome not only results in pelvic congestion, but can also cause symptoms like hematuria and proteinuria.[39] Thus, other studies have also investigated treatment options; left renal vein transposition is the most commonly used technique and it has shown favorable results, with only two reported incidents of retroperitoneal hematoma, two of ileus, and one deep venous thrombosis.[38,39]

Treatment of iliac vein compression syndrome

Iliac vein compression can also lead to abdominal complaints *(Figure 3)*, which was investigated by Daugherty et al.[40] A total of 18 patients received a stent in their left common iliac vein, 1 was done in conjunction with coiling of the left ovarian vein, and 1 patient underwent stenting of the suprarenal inferior vena cava. At a median follow-up of 11 months (range, 1-59 months), 15 patients (79%) were asymptomatic and 4 (21%) reported substantial improvement in complaints. The median venous clinical severity score before the intervention was 7 (range, 0-10) and decreased to 3.5 (range, 0-9) after the intervention. This retrospective study included patients with both pelvic complaints that severely affected their quality of life and proven nonthrombotic venous outflow obstruction on duplex ultrasound and computed tomography. Patients who also had lower extremity complaints that were more important than the pelvic complaints were excluded. If intravascular ultrasound and venography confirmed a nonthrombotic lesion, a stent was placed. A total of 10 patients initially presented with lower leg complaints, but after anamnesis it became clear that pelvic complaints were more relevant than lower leg pain. A history of hysterectomy was present in 8 patients, which highlights the fact that hysterectomy does not necessarily lead to a reduction in PCS complaints.

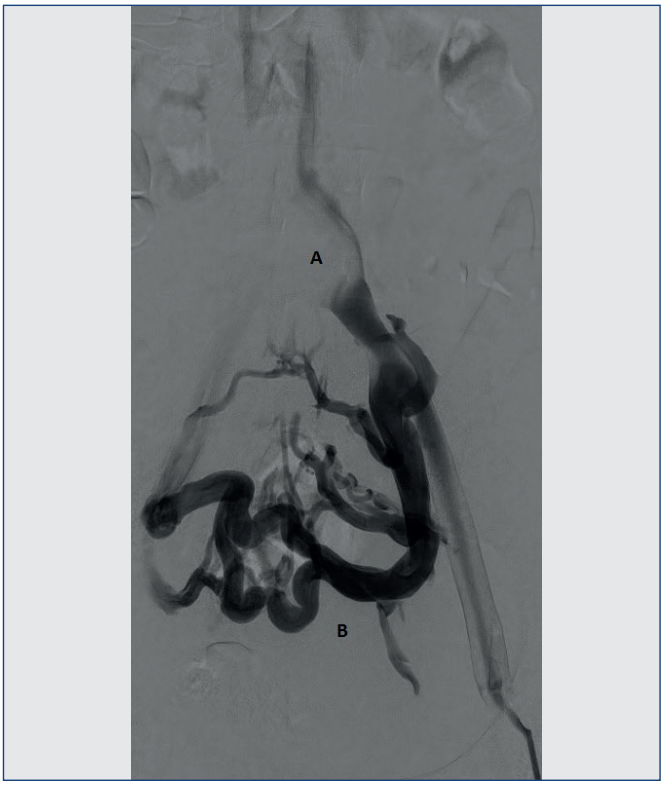

Figure 3. Venogram of the left venous iliac tract.

***A.** Lack of contrast filling in the left common iliac vein due to compression of the overlying iliac artery. **B.** Extensive collateral formation in the pelvis.*

Also, 7 ovarian veins were found to be incompetent, but only 1 ovarian vein needed treatment.

Stenting for iliac vein compression has been studied a lot for lower extremity complaints. In these studies, few complications were encountered and patency rates as high as 100% have been reported.[41,42]

Discussion

Several treatment options exist for PCS. Medical treatment with MPA or GnRH agonists can be considered, although a considerable amount of patients do not experience adequate relief from their complaints and side effects are frequent and uncomfortable.[5,7] In the past, the next step was hysterectomy with salpingo-oophorectomy; however, efficacy of this procedure is unclear as Beard et al[6] reported good clinical results, while Chung et al[16] did not. The high prevalence of hysterectomies in patients with PCS in the study by Daugherty et al[40] could be an indication that such a surgical procedure should be avoided if possible, especially considering the invasiveness of the procedure compared with endovascular approaches.

Chung et al[16] did show a significant effect of ovarian vein embolization on pelvic pain reduction. Although this was the only randomized controlled trial, several large studies have shown a positive effect by ovarian and/or internal iliac vein embolization on pelvic pain, dyspareunia, and menstrual pain.[26,28,30] Patience may be required as the duration before improvement can be 9.3 to 13.5 months, with earlier improvement in those with less severe complaints.[28] Furthermore, concurrent lower limb complaints and urinary urgency have been identified as independent risk factors for incomplete treatment success.[30]

Reports on unresponsiveness to PCS treatment vary; 6% to 53% of patients show no improvement.[5] Although the overall heterogeneity and methodological imperfections can partly account for this variation, it is likely that a psychosocial component should not be overlooked. Patients who scored high on the revised social readjustment rating scale seem to respond less to embolization treatment,[16] whereas patients with psychotherapy appear to have a longer lasting effect from the hormone treatment.[10] Therefore, unresponsiveness to treatment should not necessarily lead to a reintervention, especially since odds of success appear to be limited.[35] Also, not all people who show signs of venous congestion in the pelvic area, present with symptoms of pelvic pain. Several studies have shown that 5% to 63% of patients in a population without pelvic pain suffer from some form of pelvic congestion.[43-46]

No recommendations can be made for a method of embolization. Coiling, foam, and glue seem to yield similar outcomes, although no proper comparisons have been performed. Thus, no clear conclusions can be drawn. It is also difficult to compare the individual effect of either ovarian vein or internal iliac vein embolization since studies have used both techniques without subanalyses. Evidence suggests that when both ovarian and internal iliac vein incompetence are present, treating ovarian vein incompetence alone does not lead to adequate relief of symptoms.[19]

The possible presence of deep vein obstruction in PCS should not be forgotten. Compression of the left renal vein or common iliac vein can lead to pelvic congestion, which can be treated by venous stenting.[38,40] Stenting of the left renal vein is not suggested as the first choice of treatment because data on this type of stenting is scarce and stent migration is frequent. However, no real conclusions should be drawn from experience in only 5 patients with one particular type of stent. New dedicated stents might be far more appropriate for left renal vein stenting, which could decrease the risk of migration and make stenting a first-line treatment. Ovarian vein embolization might be effective in the presence of renal vein entrapment,[23] yet this is not the preferred hemodynamic option. No data exist about the effect on kidney function, which might be impaired since renal vein entrapment pertains to an outflow obstruction of a highly perfused organ. Before performing ovarian vein embolization, it is probably essential to evaluate whether a Nutcracker or iliac vein compression is present, because occluding the ovarian vein is, in fact, occluding the outflow of the renal vein or occluding the collateral circulation developed due to the iliac vein obstruction. It seems logical to treat obstruction first, if simultaneously present, and treat persistent symptomatic incompetence second, as collateral function has been suggested to be important.[47]

In conclusion, pelvic congestion syndrome is a poorly understood disease with several treatment options. Percutaneous endovenous techniques seem to be the best choice as an initial treatment option. However, psychosocial factors appear to weigh heavily on treatment outcomes. Future research should focus on a number of aspects. First, reproducibility of treatment procedures and randomized controlled trials should determine whether treatment of pelvic venous obstruction or incompetence is useful in relieving chronic pelvic pain. Second, properly designed studies should identify the importance of treating obstruction before incompetence. Finally, the additive effect of psychotherapy should be investigated.

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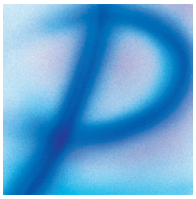

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Articles should discuss a topic of current interest, outline recent knowledge on the subject, provide personal views and analyze the different opinions regarding the topic, and cite the latest data from the literature. The article should contain:

- **A title page** that includes a concise and informative **title,** the **full names of all the authors** (first name, middle initial, and last name), the **highest academic degrees of all authors** (in country of origin language) and **affiliations** (names of department[s] and institution[s] at the time the work was done), a **short running title** (no more than 50 characters and spaces), 5 to 10 **keywords**, the **corresponding author's complete mailing address,** telephone number, and e-mail address.
- **An abstract (200 to 230 words).**
- **A main text (2800 to 3200 words, not including the references**). All references should be cited in the text and numbered consecutively using superscript Arabic numerals. Please do not use the author-date system (see the section on references below).
- A current **color photograph** (head and shoulder) of the corresponding author (TIF or JPG files at 300 dpi).
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Journal article with more than 6 authors: Sessa C, Perrin M, Porcu P, et al. Popliteal venous aneurysms: a two-center experience with 21 cases and review of the literature. *Int J Angiol*. 2000;9:164-170.

Journal article that has been accepted and published online ahead of print: Gulcu A, Ozutemiz C, Ugurlu B, Kose T. Duplex ultrasonography findings are not related to menstrual cycle phases in women with early symptoms of lower extremity chronic venous disease. *J Clin Ultrasound*. 2015 July 16. Epub ahead of print.

Article in a supplement: Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al. Chronic venous insufficiency: dysregulation of collagen synthesis. *Angiology*. 2003;(suppl 1):S13-S18.

Chapter in a book: Coleridge Smith PD. The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum*. 2nd ed. London, UK: Arnold; 2001:309-321.

Web-based material: Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. American Heart Association, 2000. http://www.circulationaha.org. Accessed October 17, 2005.

Presentation at a conference: Jantet G. Epidemiological results of the RELIEF study across different continents. Paper presented at: 15th World Congress of the Union Internationale de Phlébologie; October 2-7, 2005; Rio de Janeiro, Brazil.

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