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GUIDELINES AND CONSENSUS
VENOUS DISEASE

EDITOR'S CHOICE

Diagnosis and treatment of pelvic congestion syndrome: UIP consensus document

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1. Introduction

The use of the term "pelvic congestion syndrome" for this medical condition is recognized as incompletely characterizing the full pathophysiology and presentations of diseases of the pelvic venous system. This is, something that both the authors of the document as well as specialists, actively involved in research of this condition, agree. Several alternative terms ("pelvic venous disorders", "pelvic venous disease".) are being proposed. However, since the final agreement on the optimal nomenclature still has not been reached, the consensus document task force members decided that the document should contain the term "pelvic congestion syndrome", which is included in the recent International Classification of Diseases and VEIN-TERM Transatlantic Interdisciplinary Consensus Document.[1]

1.1 Background

In the mid-19th century, the association between chronic pelvic pain (CPP) and the presence of varicose veins in the utero-ovarian plexus was noted by Richet who also described the presence of pelvic varices.[2] In 1949, Taylor first described pelvic venous enlargement as a cause of CPP,[3] which, more recently, was shown by Hobbs[4] in 1976 and Lechter[5] in 1985. In 1990 Hobbs described a method of ovarian vein ligation via a retroperitoneal approach.[6] In 1991, Beard *et al.*[7] presented data from 36 women, to whom, after unsuccessful conservative treatment, underwent hysterectomy with bilateral salpingo-oophorectomy with 1-year prolonged good pain relief. In 1995 Mathis *et al.*[8] and in 2003 Gargiulo *et al.* [9] reported outcomes of laparoscopic ligation of the ovarian veins with good short-

term results. In 1993 Edwards *et al.*[10] presented the first case of treatment of pelvic congestion syndrome (PCS) by embolization. During the current century this procedure has become the method of choice in the treatment of PCS. However, only few articles have been published that report the long-term results.[11] Only single studies regarding conservative treatment of PCS have been published: hormone therapy in 2001[12] and venoactive therapy in 2009.[13] Many women with PCS spend many years trying to get an answer as to why they have this CPP.[14] Living with CPP is difficult and not only affects the woman directly, but also her interactions with her family and friends, as well her general outlook on life. In such cases, because the cause of the pelvic pain is not diagnosed, no therapy is provided even though there is therapy available.

1.2 Definition of PCS

Chronic pelvic pain is generally defined as non-cyclic pelvic pain greater than 6 months in duration. Chronic pelvic pain of venous origin is generally referred to as pelvic congestion syndrome although historically this has had several definitions. One of the first definitions of PCS was described by Taylor[3] as an increase in the size and number and size of intra-pelvic venous structures. In 1984, Beard defined PCS as a condition characterized by visible congestion of pelvic veins on pelvic venography in multiparous, premenopausal women with a history of CPP for more than 6 month.[7] In 1997, Monedero[15] introduced sub-diaphragmatic venous insufficiency as a unifying term of PCS and chronic venous insufficiency of the lower extremities. There are many different terms which were used to describe PCS: "Taylor's syndrome," "Congestion-fibrosis syndrome," "pelvic vein incompetence," "female varicocele" etc.[5, 6, 10, 13, 14] Nowadays, a more recent definition of PCS was stated in the VEIN-TERM Transatlantic Interdisciplinary Consensus Document,[1] which described PCS as a "chronic symptoms which may include pelvic pain, perineal heaviness, urgency of micturation 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".

1.3 Prevalence of PCS

PCS that is, chronic pelvic pain of venous origin is one of the most important causes of CPP in women and is the result of pathological venous hemodynamics in the ovarian and pelvic veins. It has been reported that as many as 39% of women experience CPP at some time in their life.[16, 17] In this group of patients in whom there are no other apparent causes of pelvic pain, an estimated 30% have pelvic venous insufficiency (PVI).[17] Ovarian vein dilatation is seen in 10% of women, up to 60% of whom may develop PCS.[18] However, it should be noted that recent work has shown that ovarian vein diameter may not precisely correlate with ovarian venous reflux, with many normally sized ovarian veins exhibiting pathological reflux, and some large ovarian veins being competent.[19] Studies show 30% of patients with CPP have PCS as the sole cause of their pain and an additional 15% have PCS along with another pelvic pathology.[20] Soysal *et al.*[12] found a 31% prevalence of PCS in a population of symptomatic women after evaluation with pelvic examination, laparoscopy, ultrasound and venography. In patients in whom intrinsic disease was discovered, the authors found that 12% also had PCS while only 1 of 30 asymptomatic patients was found to have dilated pelvic veins. There is an increasing incidence with the number of pregnancies. This may explain the relative infrequency in the USA after one or two pregnancies. In South America and elsewhere the condition is extremely common after 7-13 pregnancies.[19] The true real prevalence of PCS is still unclear and large population based epidemiological studies are needed.

2. Pathophysiology of PCS

2.1 Etiology of PCS

Pelvic congestion syndrome most commonly effects women of reproductive age (20-45 years) and incidence is strongly related with numbers of pregnancies. Pregnancy is associated with a 60% increasing of the capacity of the pelvic veins, with associated dilation of the ovarian veins.[21] The vasodilatatory effect of hormonal changes during pregnancy (elevated levels of estrogen and progesterone) also likely lead to ovarian venous dilation, perhaps accounting for the very rare occurrence of pelvic congestion syndrome in postmenopausal women. It is likely that the ovarian veins fail to return to normal size after pregnancy and may become associated with the development of valvular incompetence.[22] However, recent work has suggested that reflux in the ovarian veins is an ascending pattern, with the valves at the top of the vein being the last to become incompetent, except in true May-Thurner Syndrome.[23, 24] It has been suggested that some anatomical conditions, such as kinking of the ovarian vein by a retroverted uterus,[16] external compression (nutcracker syndrome, May-Thurner Syndrome, retroperitoneal mass, etc.) may be associated with the development of pelvic

congestion symptoms. Some authors described a possible association with psychosocial conditions.[25] They reported significant correlation between some social arrangement, paternal parenting and patents of hostility in patients with PCS.

2.2 Hemodynamic changes in PCS

Symptoms associated with PCS presumably arise from pelvic venous hypertension with distension of the per-uterine venous plexus. As discussed above, this is likely related to a number of hormonal, genetic, and hemodynamic factors associated with venous dilation, decreased elasticity of the vein wall, and ultimately valvular incompetence. PCS has been classically associated with incompetence of the ovarian veins. However similar pelvic venous hypertension and symptoms can result from primary internal iliac vein reflux or from compression of the left common iliac vein ("May-Thurner" Syndrome) or left renal vein ("Nutcracker Syndrome") with increased venous pressure transmitted to the peri-uterine venous plexus through the left ovarian and left internal iliac veins respectively. In addition to symptoms of chronic pelvic pain, PCS may also be associated with lower extremity varicose veins, either in a typical axial saphenous distribution or in atypical locations including the vulva, perineum, and posterior thigh. Such varices arise from the development of venous reflux in the distal tributaries of the internal iliac veins with transmission of venous pressure through the escape points in the pelvic floor to the lower extremity veins. Generally, the right ovarian vein is subject to pregnancy-related changes, and often serves as a shunt, relieving the effects of incompetence of the left ovarian vein.[26] The hemodynamic changes of collateral pathways vary significantly according to the causal mechanism and the site of occlusion or stenosis. The abnormal dilatation of pelvic veins may occur either because of restricted or increased blood flow.[27]

2.3 Structural changes in PCS

Anatomic studies have shown that approximately 13-15% of women have no valves in the left ovarian vein. In autopsy series valves in the upper portion of ovarian veins were absent on the right side in 6% and on the left side in 15%.[28] As in chronic venous disease of the lower extremities, venous hypertension in pelvic veins increases the expression of matrix metalloproteinases, which degrade the underlying endothelium and smooth muscle. These changes impair the ability of veins to constrict and relax leading to increase venous pressure, which further promotes endothelial cell injury by triggering leukocyte infiltration and inflammation, resulting in chronic venous distention and reflux.[29, 30] The histology of pelvic varicosities is similar to that of varicose veins elsewhere, including fibrosis of the tunica intima and media, muscular hypertrophy and proliferation of capillary endothelium.[29] Women with PCS tend to have larger uterus and more cystic changes in their ovaries than healthy women, because of congestion and estrogen overstimulation. Ultrasound studies have shown a significant increase in uterine thickness and size in pelvic congestion.[28] Polycystic changes of the ovaries in patients with PCS were different from those of women with classic polycystic ovary syndrome. Patients with PCS and with polycystic changes of the ovaries were noted to be hirsute or amenorrhoeic. Cystic changes in the ovaries ranged from a classic polycystic appearance to the presence of clusters of four to six cysts of 5-15 mm in diameter in bilaterally enlarged ovaries. The significance of the cystic changes in the ovaries remains unclear.[31] The animal-based model suggests that uterine and ovarian veins have disproportional sensitivity to ovarian-produced hormones. During a normal menstrual cycle, the ovarian veins are exposed to a nearly 100-fold higher concentration of estrone and estradiol compared with peripheral plasma.[32]

3. Diagnosis

3.1 Clinical evaluation

Patients with PCS typically present between 20 and 45 years of age. There is no known genetic or ethnic predisposition, though the entity is more common in multiparous women. Pelvic pain is typically dull and aching in nature, non-cyclical and can be exacerbated by postural changes, walking and sexual intercourse and, also, during menstruation.[31, 32] Pain is present more the 6 month (without evidence of inflammatory disease) and except the pelvic may be exposure in lumbar (low back pain), sciatic, sural or other regions. Dyspareunia (pain during or after coitus) with 6 or more points by VAS (Visual Analogue Scale) usually radiating out to the anus and have variable duration, up to 24 hours.[14] Other clinical manifestations of pelvic congestion syndrome may be various and it can be shown as a symptoms of different systems: gynecological (dysmenorrhea, vaginal discharge), urological (disuria, urinary frequency), gastroenterological (nausea, bloating, abdominal cramps, rectal discomfort).[33] More seldom a patient with pelvic varicosities may present with renal colics, due to ureteral compression by a dilated ovarian vein. This is known as "ovarian vein syndrome".[32] In most cases neurological and psychosomatic symptoms also present

(lethargy, depression). During the physical examination attracts attention cervical motion tenderness or point tenderness over the ovaries or uterus on bimanual examination.[34] The combination of postcoital ache and ovarian point tenderness is reported to be 94% sensitive and 77% specific for pelvic venous insufficiency when confirmed by venography.[35-38] During the bimanual examination reveals tenderness without indurations or masses.[37] An important step in physical examination is to evaluate varicose vein network, which may be present on perineal, vulval, gluteal or posterior thigh areas. By the Monedero *et al*.,[15] vulval varicosities developed because of reflux in left and right ovarian and pudendal-obturator veins in case of pelvic floor insufficiency, whereas perineal, gluteal and posterior thigh varicosities mostly generated by the reflux from internal iliac vein. There is a strong association between hemorrhoids and internal iliac vein reflux. Untreated reflux may be a cause of subsequent symptomatic haemorrhoids.[39] Vulvar varices occur in about 10% of pregnant women. They are rare during a first pregnancy and generally develop during 5th month of a second pregnancy. The risk is increases with the number of pregnancies. Their incidence is underestimated for three reasons: 1) women are embarrassed to talk about them; 2) they are not adequately sought with the patient in the standing position during the physical examination of month 6 of pregnancy and the first month after delivery; 3) most often, they are asymptomatic. Vulvar varicosities tend to disappear spontaneously after delivery and rarely persists one-month later.[37]

3.2 Noninvasive test

The primary goal and utility of ultrasound (US), magnetic resonance (MR) imaging, computed tomography (CT) in the workup of PVI is to exclude a concurrent pelvic pathologic process. Although cross-sectional imaging may demonstrate pelvic venous ectasia.[38] The sensitivity of these methods of diagnosis for pelvic congestion syndrome is low — 59, 20 and 13% for MRI, US and CT, respectively.[15]

3.2.1 Ultrasound assessment

Sonography is regarded as a first line investigation into pelvic congestion syndrome, it is non-invasive, easily accessible and inexpensive, it also allows for the exclusion of other pelvic pathology.[36] Depending on the initial referral, there are different first-line imaging modalities. Patients from the gynecology department usually are screened with transvaginal ultrasound. Patients referred from the vascular surgery department have either been screened with transabdominal ultrasound.[38]

3.2.1.1 Transabdominal Duplex ultrasound

Transabdominal ultrasound is practically first step in evaluation for pelvic congestion syndrome that can exclude intrinsic pelvic conditions, demonstrate pelvic varicosities, and suggest ovarian vein insufficiency,[40, 41] but, unfortunately, at observational transabdominal gynecological ultrasound investigation of women many doctors do not pay attention on existence of pelvic vein varicosities, because in difference of standard assessment, pelvic vein evaluation better to do when bladder is voiding and do not compress pelvic varicosities and visualization is better. Despite that transvaginal ultrasound more correctly show enlargement and congestion of pelvic veins, transabdominal ultrasound have a great diagnostic value because of direct visualization of left ovarian vein. An ovarian vein diameter of 6 mm on transabdominal ultrasonography has been reported to have a 96% positive-predictive value for pelvic varices.[42] Flow parameters by Doppler have the crucial role for future adequate treatment options: exist of high antegrade flow in ovarian vein or reversal flow in internal iliac vein show that the etiology of venous congestion is secondary due to intravascular (thrombotic) or extravascular (compression) factors.[11-15] Presence of this factors (left renal vein compression, iliac vein compression, arterial-venous malformations, pelvic hypervascular masses, portal hypertension, etc.) again must be evaluate with transabdominal ultrasound, also as surely have to exclude other pathologies of pelvic origin. During the transabdominal ultrasound examination necessary to check structural changes in uterus and ovaries: about half of patients with pelvic congestion syndrome had cystic changes in their ovaries, ranging from classic polycystic ovary syndrome to clusters of cysts in bilaterally enlarged ovaries.[43] However, this can be difficult to assess using transabdominal ultrasound in which case transvaginal ultrasound is superior. In one third of patients the volume of the uterus is considerably increased compared to healthy population.

3.2.1.2 Transvaginal Duplex ultrasound

The transvaginal approach is considered to be the examination of choice since it offers better visualization of the pelvic venous plexus compared to transabdominal ultrasound, and is not hampered by patient habitués or undisplaceable bowel gas.[41] Another advantage of ultrasound examination is the possibility to perform it on standing position and also evaluation of venous filling during Valsalva maneuver. The sonographic appearances of normal pelvic venous plexus are one or two straight tubular structures with a diameter of less than 5 mm. However,

the sonographic appearance of the ovarian and pelvic varicose veins are multiple dilated veins around the ovary and uterus with a venous Doppler signal of varying amplitude. The presence of circular or linear venous structures with a diameter greater than 5 mm is indicative of pelvic varicosities.[41] Reversed caudal blood flow may be seen in the ovarian veins and dilated arcuate veins may be seen crossing the myometrium.[42, 43] By the Monedero *et al.*,[44] there are following possible variations of ultrasound imagine during transvaginal examination in possible existence of pelvic congestion syndrome: 1) pelvic varicose veins up to 7 mm without continuous flow; 2) pelvic varicose veins up to 7 mm with substitute continuous flow; 3) no pelvic varicose veins. Park *et al.*[45] described the criteria for the ultrasound diagnosis of pelvic congestion syndrome: 1) normal diameter of pelvic vein are less than 4 mm; 2) tortuous aspect of ovarian veins; 3) pelvic varicosities, up to 6 mm; 4) slow blood flow or reversed caudal flow; 5) dilated arcuate veins in the myometrium, communicating between bilateral pelvic varicose veins; 6) polycystic changes in the ovaries.

3.2.1.3 Duplex ultrasonography of the veins of lower limbs

Duplex-ultrasonography of the veins of lower extremities is the necessary part of the imaging protocol for improved evaluation of pelvic congestion syndrome, especially in the presence of atypical varicose veins. Atypical varicose veins located on the posterior and lateral aspect of the thigh are quite pathognomic for pelvic venous insufficiency, which can also cause non-sapheno-femoral reflux in the groin.[45-48] In one study, authors show that 70% of patient which have the pelvic veins more than 5 mm in diameter, they observed venous insufficiency in various degrees in the CFV, DFV, SFV, LSV, SSV and PV. While lower limb venous insufficiency was most frequently seen in the CFV (in 52% of the women), it was also seen in descending order: in the LSV (23%), PV (10%), DFV (6%), SFV (6%), and SSV (3%).[26] One of the leading cause of the presence of varices after operative treatment (PREVAIT) is the tactical errors to all options of operative treatments of chronic venous disease of lower extremities, which includes wrong or incomplete diagnosis of the extent and/or location of varices, source of reflux, identification of deep venous anomalies including pelvic reflux.[49] Balian *et al.*[26] consider necessary to perform venous examination of the lower limbs (with a linear transducer of at least 7.5 MHz) is carried out prior to, or concomitantly with, examination of the pelvis when there are varicosities. It is necessary to establish mapping of abnormalities and to assess the relative impact of pelvic hemodynamic abnormalities.[24] Features that suggest PVI may include the existence of veins of abdominal origin (superficial circumflex, superficial epigastric vein) or subinguinal origin (external pudendal vein, posterior communicating vein), emptying into the incontinent superficial venous network.[48-50]

3.2.2 Cross-sectional CT

Cross-sectional imaging, particularly, CT characterized by the smaller diagnostic importance than other diagnostic methods. First, it cannot be used as a routine diagnostic method as ultrasound and, on the other hand, does not give information about hemodynamic changes in pelvic veins. With the use of multi-detector CT, a larger region can be imaged in the same phase as compared to spiral CT. Reflux of the contrast material to the left renal vein generally occurs in the corticomedullary phase, *i.e.* the arterial phase. When the contrast material is in the arterial system and the renal veins in the arterial phase, simultaneous opacification of the ovarian veins shows the reflux to the ovarian vein.[28-53] CT scans are often ordered for abdominal pain, which show venous varices in the area of uterus or in the pelvis. In addition, careful review of the images often shows a large, dilated ovarian veins. On CT the varicosities are isodense to other abdominal veins on postcontrast imaging.[42] Computed tomography has the capability to exclude other pelvic pathologies.[51]

3.2.3 Magnetic resonance venography

In comparison of CT, magnetic resonance venography (MRV) has the superiority because of the absence of radiation and therefore is a priority cross-sectional diagnostic method. However, it is conventionally performed with the patient in the supine position causing underfilling of the varices, and artefacts metallic coils after embolization limit the use of MRV for follow-up imaging.[52] Pelvic varices can be visualized efficiently in 3-dimemensional T1-weihted gradient echo MR sequences after the administration of intravenous gadolinium, and flow in the pelvic varices appears in high signal intensity.[54] Pelvic varicosities are identified as enlarged tortuous tubular structures in the trajectory of the ovarian veins, around the adnexa, and in the pelvic floor. Furthermore, the renal veins can be assessed for signs of compression (Nutcracker syndrome), as well as the common and/or external iliac vein.[41] Various authors present criteria's for cross-sectional imaging diagnosis of pelvic congestion syndrome: 1) grade I venous reflux: early filling of left ovarian vein and/or left parauterine veins; 2) grade II venous reflux: grade I reflux + right

ovarian gonadal vein reflux (left/right); 3) identification of four ipsilateral pelvic veins with a least one measuring more than 4 mm; 4) ovarian vein diameter more than 8 mm.[50-54]

3.3 Invasive tests

3.3.1 Catheter-directed selective venography

Catheter-directed retrograde selective venography of ovarian and internal iliac veins is method of choice for the diagnosis of pelvic venous pathology. This is done to confirm the diagnosis, assess the venous anatomy, especially the collateral venous supply, and allow planning of embolization and coil selection.[47] Confirmation of pelvic congestion syndrome via catheter-directed venography before embolization is essential. Venography can be done *via* cubital, jugular or femoral access with use classic Seldinger method. For the catheterization of left renal vein various authors recommend different types of 4-6 F catheters (Simmons I, Simmons II, Cobra II, Multipurpose etc.) over a hydrophilic guidewire. Manual ejection of iodinate contrast material must be done in semi-erect position of patient and/or during Valsalva maneuver. The right ovarian vein is catheterized directly via inferior vena cava and similarly assessed. Both internal iliac veins also must be evaluated very carefully. Laborda *et al.*[55] consider it necessary also to evaluate the hypogastric, external iliac and common femoral veins. During the evaluation, some authors recommend to pay special attention on opacification in reno-caval and ilio-caval segments for looking the obstructive syndromes. Particularly, Monedero *et al.*[11, 15] consider very important to measure reno-caval and ilio-caval pressure gradient to detecting left renal vein (Nutcracker) and left iliac vein (May-Thurner) compressive syndromes. Catheterization of bladder also recommend to avoid failure of visualization. In case of atypical varicose veins of lower extremities to perform the bilateral descending venography of femoral veins are necessary. Diagnostic criteria for pelvic congestion syndrome are following: 1) an ovarian vein diameter more than 6 mm; 2) contrast retention more than 20 seconds; 3) congestion of the pelvic venous plexus and/or opacification of the ipsilateral (or contralateral) internal iliac vein, or 4) filling of vulvovaginal and thigh varicosities.[42]

3.3.2 Intravascular ultrasound

Using of intravascular ultrasound (IVUS) for diagnosis of pelvic congestion syndrome is very rare and mostly performed for detecting of compressive syndromes (Nutcracker, May-Thurner) or in post-thrombotic damage of the veins, *i.e.* for pelvic congestion syndrome IVUS is diagnostic method, preciously, determine the obstructive etiology. Some authors consider necessary using IVUS during stent therapy of iliac vein compressive syndrome either as diagnostic procedure and during the stent placement.[56] IVUS examination were consider in patients who had severe symptoms interfering with work or daily living and had failed conservative therapy.[57] Patients undergoing IVUS fell into one or two broad categories: 1) iliac vein pathology was suspected (estimated 80% of limbs) from one or more investigations, whether associated with significant distal reflux or not; 2) results of investigations for iliac vein obstruction were negative (estimated 20% of limbs) but clinically suspected because detected distal reflux either minimal (*e.g.*, single segment reflux) or altogether absent in the context of severe symptoms.[58] IVUS-guided endovascular repair influenced decisions on additional therapy in 50% of the patients with iliac vein obstructive syndrome.[56] Lapropoulos recommends using IVUS along with venography and reno-caval gradient measurement in diagnosis of Nutcracker syndrome.[59]

3.3.3 Laparoscopy

The sensitivity of laparoscopy for diagnosis of pelvic congestion syndrome is approximately 40%.[18] Laparoscopy is often used in patients with chronic pelvic pain in search of a specific diagnosis and in many gynecological centers it is initial method of diagnosis. In case of pelvic congestion syndrome, diagnostic findings during laparoscopy include existence of prominent enlarged broad ligament veins and may reveal pelvic varices.[15] However, because the examination is done supine and requires insufflations of CO2 gas, there may be compression of varices if present, thereby masking the diagnosis of pelvic congestion syndrome.[60] Many Ob/Gyn physicians now opt to do the full laparoscopic view of the pelvis before insufflating with CO2 gas; pelvic varices can then occasionally be seen filling at this point. Despite these efforts, laparoscopy can still be negative in 80% to 90% of patients who do have pelvic congestion syndrome.[34]

3.4 Differential diagnosis with other causes of chronic pelvic pain

As the historical and physical findings associated with pelvic congestion syndrome are non-specific, the list of differential diagnoses is large. They include gynecological causes, disorders originating from the urinary tract or gastrointestinal tract, musculoskeletal causes, neurologi-

cal disorders and mental health issues.[37] Particularly, for the confirmation the diagnosis of pelvic congestion syndrome must be excluded other pathologies of pelvis such as: fibroids, adenomyosis, endometriosis, pelvic inflammatory disease, ovarian and fallopian tube diseases, pelvic tumors, cystitis, inflammatory bowel diseases and adhesions, pelvic arterial-venous malformations, portal hypertension, etc.[37] Generally, the diagnosis of pelvic congestion syndrome can be made by excluding other causes of chronic pelvic pain.

4. Classification of PCS

The female pelvic venous anatomy and hemodynamics are complex and are only beginning to be understood. Although PCS has been historically associated with primary incompetence of the ovarian veins, it is clear that chronic pelvic pain of venous origin may also be associated with internal iliac venous reflux or obstruction of the left renal or iliac veins. The imperfect results associated with ovarian vein embolization may be at least partially related to inaccurate diagnosis of the underlying pathology responsible for the patient's symptoms. There is a clear and desperate need for better classification of pelvic venous pathology. Several classification systems have been suggested. Monedero *et al.*[15] presented a classification of PCS based on hemodynamic changes (pressure alterations) in pelvic veins: 1) centrifugal (retrograde) collateral systems formation; 2) centripetal (anterograde) collateral systems formation; 3) one of the listed hemodynamic conditions with leaking to the lower limbs. This classification has a great importance for adequate planning of invasive treatment of PCS. Greiner *et al.*[30] presented a classification of pelvic venous anomalies, which is based on the etiology of venous anomalies: type 1: reflux pathology secondary to valvular or parietal venous anomalies (without pelvic or supra pelvic obstruction to venous flow); type 2: substitute pathology secondary to stenosis or obstruction in a draining vein with supra pelvic or pelvic obstruction; type 3: venous anomalies secondary to a local extrinsic cause.

5. Treatment

5.1 Medical therapy

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

5.1.1 Symptomatic (pain-relief) treatment

Psychotropic drugs, such as gabapentin and amitriptyline, have been shown to be effective in treating CPP. 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.[21] Perry *et al.*[22] 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. Nonsteroidal anti-inflammatory drugs are an acceptable first-line treatment. They may offer some short-term relief while patients await further investigations or a more permanent treatment. However, non-steroidal anti-inflammatory drugs are not a long-term solution for the patient's with CPP.[23]

5.1.2 Hormonal therapy

Medoxyprogesterone acetate (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 long term 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.[12] 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.[28] 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.[31] Gonadotropin-releasing hormone (GnRH) agonists have also been used for the treatment of PCS. An injectable GnRH agonist, also known as Goserelin acetate is used to suppress production of the sex hormones testosterone and estrogen, particularly in the treatment of breast and prostate cancer.[31] The synthetic steroid Implanon is a single-rod, non-biodegradable implant that contains and releases etonogestrel (3-keto-desogestrel), a progestin that is used as a long-term contraceptive. Patients with pure PCS due to venous stasis may benefit from this kind of treatment.[61-65]

5.1.3 Venoactive drugs

Venoactive drugs, particularly the micronized purified flavonoid fraction (MPFF*) have a protective and tonic effect

on the venous and capillary wall, which increases venous tone.[13] Simsek *et al.*[66] conducted a randomized controlled crossover trial of 20 patients, where randomization was performed in 2 groups of 10 patients. 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. 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. In a trial by Gavrilov *et al.*[67] in women suffering from CPP 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. 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.

5.2 Surgical treatment

Ovarain vein ligation, either retroperitoneal or laparoscopic has historically been suggested as a treatment for primary ovarian vein incompetence. Excellent results following extraperitoneal ovarian vein resection were reported in 57 patients with moderately severe symptoms.[68] At least some evidence suggests that bilateral ovarian vein resection may be more effective than unilateral approaches. Hobbs has emphasized the importance of resecting the ovarian vein from the confluence with the left renal vein or IVC past the confluence of the ovarian tributaries in the pelvis.[6] However, as these procedures are more invasive than endovascular embolization and they require a general anesthetic with a longer recovery period, they are rarely used at present. Furthermore, as surgical ligation can only interrupt the refluxing pathway at a limited number of locations, recurrences may be more common than after endovascular approaches. Hysterectomy with salpingo-oopherectomy has been performed in the past. However, its effect is not been proven convincingly and removal of the reproductive organs is not advised.

5.3 Sclerotherapy

Embolization of the incompetent veins and the periuterine venous plexus is used to obliterate refluxing varicose vein. To occlude the peri-venous plexus, sclerotherapy often performed injecting foam or liquid sclerosant as distally as possible to occlude the pelvic venous plexus.[69] An occlusion balloon placed just above the true pelvis, where the tributaries of the main ovarian vein join aids the filling of the plexus. 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 wards a few coils are placed in the lower part of the ovarian vein, the balloon is deflated and withdrawn a few centimeters and sclerosant injection repeated with periodic coil insertion until about 5 cm from the termination of the gonadal vein.[15]

5.4 Endovascular treatment

5.4.1 Transcatheter embolization therapy

As previously stated, ovarian vein embolization has a low rate of morbidity or complications and has largely replaced open surgical intervention for symptomatic ovarian vein incompetence. The first reported case of uterine-ovarian varices embolization was described by Edwards in 1993.[10] Since then, many authors have used this procedure, with positive results in most patients.[33, 60, 66-73] The aim of embolization is to occlude insufficient venous axes as close as possible to the origin of the reflux. In pelvic venous disorders these will be the gonadal axes, pelvic varicose veins and insufficient tributary branches of the internal iliac veins.

Ovarian vein embolization is generally performed under local anesthesia or moderate sedation using fluoroscopic guidance on a radiological tilt table.[70] A variety of access points have been utilized including the basilic veins, the right internal jugular vein and the femoral veins. As the course to the ovarian veins is shorter and straighter, many prefer the right internal jugular approach.

Using fluoroscopic controlled guidance and a multipurpose catheter left renal and left iliac venograms is usually the first step, are often initially performed to evaluate compressive syndromes. As these compressive lesions of the renal and iliac veins usually occur in an antero-posterior plane, findings on single plane venography may include flattening of the vein, contrast attenuation, and opacification of collaterals including the left ovarian vein in the case of renal vein compression. Although multiplanar venography may be helpful in left common iliac vein compression, the course of the left renal vein is often best demonstrated in 3 dimensional rotational views. However, if compressive lesions are clinically suspected, as discussed above, these are often best demonstrated with IVUS.[56, 59]

The next step is to selectively cannulate the gonadal and internal iliac veins. The left gonadal vein is a tributary of the left renal vein and catheterization of this vein is usually performed first. The right gonadal vein is a tributary of the IVC just below the right renal vein and is often catheterized next. Contrast medium is injected in the vessel of interest and the patient (instructed before the procedure) is asked to perform a Valsalva maneuver, to evaluate for reflux. Tiling 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 contrast generally pools in the pelvic varicosities after the injection.[46] When an abnormal vein is encountered, treatment is usually performed before evaluating the next vein.

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. However, even in the presence of internal iliac reflux, antegrade flow may preclude adequate visualization of caudal varices and escape points. A compliant occlusion balloon inflated in the internal iliac vein just proximal to the confluence with the external iliac vein can be very helpful in demonstrating the distal tributaries and pelvic escape points. If identified, these tributaries can be individually selected and treated by advancing the complaint balloon catheter over a glide wire[68-]. In cases where such reflux is found, it is very important to occlude these vessels in order to avoid incomplete clinical improvement.[15]

Once identified, pathologically dilated axes with retrograde flow are mechanically occluded. A variety of mechanical devices including coils, with or without sclerotherapy, and cyanoacrylate glue have been reported in the literature. Unfortunately, solid data supporting the superiority of one technique over another is lacking. These coils must be of radiopaque materials, to allow fluoroscopic control. Coils are among the most commonly used devices for mechanical occlusion. Embolization is typically performed using a "sandwich" mixed technique, which combines metallic devices with 2% athoxisclerol foam (prepared according to Tessari's method during the procedure).[73]

While allowing the sclerosant to dwell within the pelvic venous plexus, a cluster of appropriately sized coils are deployed at the caudal end of the dominant trunk just above the confluence of tributaries. The catheter is then withdrawn several centimeters within the ovarian veins and additional sclerosant instilled followed by a second cluster of coils. The procedure is then repeated at intervals with the last cluster of coils deployed just below the confluence of the ovarian vein with either the left renal vein or IVC. Although lacking robust supporting evidence, this technique offers the potential to treat the multiple small tributaries that are often associated with the ovarian veins and may function as a source of recurrence.

After that, internal iliac veins should be investigated and, if necessary, treated. In the presence of leak points to the lower limbs and/or connections of internal iliac veins with lower peri-uterine varicose veins, selectively cannulation and embolization with coils and or sclerosants should be performed.[17] Most anecdotal experience suggests that the risk of coil migration is substantially higher in the internal iliac tributaries and careful attention to sizing and technique is required. Others have used sclerosants alone, often instilled below an occlusion balloon, to avoid the risks of coil migration. It is, however important to eliminate all sources of abdominal-pelvic reflux, in order to minimize the risk of inadequate treatment or recurrence of PCS symptoms.[69]

5.4.2 Stent therapy

The rational behind placing a stent to treat PCS is to relieve venous hypertension in the larger pelvic veins and the pelvic venous plexus. First, we need to understand how this condition of increased pressure develops. Principally, venous hypertension is either caused by hydrostatic pressure build-up or an upstream outflow obstruction. Where normally an antegrade flow drains the pelvic veins, now a retrograde flow or reflux into the internal iliac vein or gonadal vein increases pressure on the pelvic venous structures and adjacent tissue. Theoretically, many acute and chronic causes may be identified, both intra- and extraluminal. Longer lasting pressure build-up may cause the venous structures to change indefinite thereby causing chronic complaints, even after the obstruction has been removed. For example, pregnancy may be seen as such a temporarily venous outflow obstruction, although additional mechanisms like vasodilation play a role. Examples of chronic venous outflow obstruction are congenital inferior vena cava obstruction and venous spurs earlier described by May and Thurner.[71] Both entities may cause retrograde flow in the internal iliac veins and venous plexus. Another well accepted cause is the retrograde flow seen in ovarian vein incompetence. Believed to be the primary origin of the pelvic complaints, much attention has been put on ovarian vein embolization to treat PCS.[70, 72, 73] The ovarian vein can however also be seen as a collateral re-

lieving pressure from the left renal vein and kidney in case of a so-called "nutcracker" phenomenon, where the left renal vein (LRV) is compressed between the superior mesenteric artery and the aorta. This should most definitely not be confused with the nutcracker syndrome, in its most typical occurrence associated with hematuria and flank pain. However, when the outflow obstruction is compensated by collaterals, most notably the gonadal vein, then these typical effects of renal vein hypertension are not obligatory. Hemodynamic significance of a LRV stenosis has been correlated with an arbitrary chosen pressure gradient >3 mm Hg between the vena cava and the LRV.[74] It has been shown that a pressure gradient <1 mm Hg is normal.[75] However, a significant LRV stenosis may thus be overlooked if compensation mechanisms relieve renal vein hypertension. The ovarian vein serves as a major venous collateral route and may induce pelvic complaints, even without classic nutcracker signs as hematuria. Regrettably, we have to derive most experience in LRV stenting from the nutcracker literature. Nevertheless, this knowledge in combination with the limited number of publications on LRV stenting for PCS helps to understand, diagnose and treat this entity. Some imaging modalities have been suggested to diagnose significant renal vein compression. CT, MRI and duplex ultrasound have shown to be sensitive to identify a significant LRV stenosis.[53, 76] IVUS is an invasive technique even more accurate and currently recommended in the diagnosis of deep venous obstructions. However, a "significant" >50% stenosis on IVUS does not inevitably mean that this obstruction is clinically relevant.[56, 58] When LRV stenosis is suspected to cause PCS a venography is still very helpful to identify collaterals and flow directions. Usually, the patient is lying supine on the angiography table and contrast dye is injected into the LRV or left ovarian vein. If ovarian vein incompetence is present, a retrograde flow might be visible towards to pelvic veins and plexus, but not necessarily. Principally, with the patient lying in the table and without hydrostatic pressure build-up a continuous retrograde flow in the gonadal vein would be unlikely. The Valsalva maneuver is a strong discriminator between primary insufficiency and an upstream obstruction. Without a Valsalva maneuver, principally there should be no "washout" of contrast from the LRV down. Only in case of a significant LRV stenosis such a washout will be visible, supporting the significance of the LRV stenosis and proposing against primary ovarian vein embolization in favor of LRV stenting. Renal vein stenting for the nutcracker phenomenon has first been proposed by Neste in 1996.[77] Renal vein hypertension was successfully treated with the implantation of a 10-mm Wall stent. Since then several case reports and retrospective studies published on the experience with self-expandable and occasionally balloon-expandable stents in the left renal vein to overcome nutcracker syndrome.[78-81] For a long time mainly Wall stents were used, foremost because no other adequate stent was available. Until 2013, all endovascular stents on the market were "arterially designed." This means that the diameters, lengths and radial outward forces of these stents did not comply with the needs in larger veins. Moreover, complications like stent migration caused by undersizing and/or stent design have been repeatedly mentioned in the literature.[74] Still, none of the stents currently on the market have been registered to treat renal vein stenosis and thus are considered off-label. Dedicated venous stents currently used to treat deep venous obstructions may also be used to treat renal vein compression. Recently, the first experience with a venous stent for treatment of posterior nutcracker syndrome was encouraging.[81]

Technique of renal vein stenting.[82-84]The ideal venous access point has been discussed before. Although the left common femoral vein (CFV) has been suggested as the ideal access site for easy renal vein catheterization, the right CFV and the right jugular vein both are good alternatives. The jugular vein access may have the disadvantage however that sheaths and stiff wires tend to pull the LRV upwards, thereby increasing the risk of stent migration. Catheterization of the LRV is straightforward with a cobra- or Simmons catheter. To introduce a guiding sheath into the LRV, the catheter can be positioned deeply into the ovarian vein and a stiff guidewire can be used for support. Large bore guiding sheaths are surely recommended to position the stent accurately in the LRV. For venous stents of sufficient diameter, a 10F sheath is not uncommon. Ample lumen should still be available for contrast injection just before stent deployment to verify the correct position. Before stent deployment, predilation with a 14-16mm balloon is recommended. As with iliac vein compression, an intraluminal spur cannot be excluded and accurate stent deployment may suffer from this. Usually, 40-60 mm stents with a diameter of 14-16 mm are used. An oversizing of 20% in relation to the normal LRV diameter is recommended.[84] Short and small diameter stents may have a greater risk of migration. Modern nitinol venous stents generally are strong enough to withstand the outside compression by the superior mesenteric artery. Differences in stent design may however convince an interventionist for a specific venous stent. Closed-cell stents may be prone to migrate, while open-cell stents may be more difficult to

deploy accurately. It has been suggested to use long stents extending far into the IVC to maximize stent stability and prevent migration. Thrombus accumulation as seen in IVC filters may however be induced by this strategy. Postdilation is advisable, however should be performed with care to prevent altering the stent integrity or position. Absence of ovarian vein filling and normalization of the renocaval pressure gradient indicated successful treatment. In the majority of published PCS cases, patients were solely treated for reflux and venous obstruction was not identified as the possible cause. Iliac vein stenting has been overlooked for many years as a treatment option for PCS until just recently. Daugherty *et al.*[85] published on 19 patients with common iliac vein or vena cava obstruction. Fifteen patients treated by stenting reported complete resolution of pelvic pain, and four reported substantial improvement. Furthermore, 14 of 17 reported complete resolution of their dyspareunia, and 3 reported partial resolution. Interestingly, only one patient required embolization of the left ovarian vein. The largest study so far has recently shown that in 80% of patients presenting with PCS a significant iliac vein obstruction was present,[86] which is surprisingly higher than previously reported. VAS Score was used to identify differences in treatment strategies. In patients with both reflux and obstruction, VAS scores were significantly reduced when stenting of the obstructive iliac lesion was performed after initial treatment of the reflux. The authors concluded that pelvic venous outflow lesions should be treated first and that ovarian vein reflux should be treated only if symptoms persist. Also it was recommended that IVUS should be performed in all patients presenting with PCS. Interestingly, in some patient no stenting was performed and the iliac vein lesion was only dilated by angioplasty. In the patient groups treated by embolization of the reflux and angioplasty or angioplasty alone, also a remarkable reduction in VAS Score was seen, similar to the stenting groups. These findings are in stark contrast to many previous reports suggesting that angioplasty is not sufficient to treat iliac vein obstructions and stenting is always necessary. Regrettably, IVUS data on area reduction before and after stenting or angioplasty were not reported. That a placebo effect played a role in these findings cannot be ruled out. We recently reported that in 80% of healthy young volunteers typical signs of iliac vein compression could be seen on angiography.[83] It remains uncertain if iliac vein compression may induce PCS later in life or that it is a coincidental irrelevant finding in most patients. In any case, it establishes again that there are still significant deficiencies in the knowledge of PCS treatment.

Technique of iliac vein stenting. Stenting for iliac vein compression has been performed worldwide over more than two decades and published copiously. The actual technique of iliac vein stenting is not very demanding. However, some aspects demand specific attention. First, the guidewire should be maneuvered through the iliac vein stenosis with care. Rarely but nonetheless catastrophic, a guidewire may find a route through a pelvic collateral and reach the IVC, not noticeable in the AP-view. Ballooning and stenting of this collateral pathway may obviously have disastrous consequences. Therefore, no matter how straightforward it may seem, oblique views during intervention are highly recommended. Different views are definitely helpful to identify significant lumen reductions. The most sensitive modality however is IVUS, which has been proven to be superior to multi-planar angiography to identify iliofemoral vein stenosis, as shown by the VIDIO Trial.[84] In addition to the common iliac vein, accurate evaluation of the entire vena cava, iliac and femoral veins with IVUS is advisable to detect any additional inflow or outflow obstructions that may influence stent patency. Predilation of the identified lesions is recommended. Predilation facilitates self-expandable stent placement by breaking up possible intraluminal spurs. After predilation, a self-expandable stent should be deployed. Although "dedicated venous stents" are currently deemed superior, the Wall stent has been mostly used with excellent results. Nevertheless, the Wall stent suffers from a few shortcomings, becoming increasingly apparent in less-experienced hands. Most young interventionists have limited experience with this stent and its specific characteristics. During deployment a significant foreshortening may occur with the risk of malpositioning. Failure to position the stent accurately may for example increase the risk of contralateral DVT by crossing the contralateral inflow. Naturally, positioning the stent too distally may result in not treating the lesion at all and obligatory restenting. In general, the modern venous stents can be positioned more accurately. However, all venous stents currently on the market have specific pros and cons with which the physician should be very familiar with before application. Postdilation is essential to ascertain full expansion of the stent and prevent migration. As mentioned before, IVUS may be helpful to detect a significant lumen narrowing in a vein. In addition, it may be used during post-stenting evaluation to determine stent position and configuration. Before stenting, the correct proximal landing spot at the level of the confluence can be identified by IVUS. However, angiographic visualization of the iliac confluence may be a more reli-

able method. After the procedure, hemostasis is achieved by applying light manual pressure on the venous access site.

Till today, there is no proof that any of the available stents show superior patency for isolated iliac vein compression. Other outcome parameters should not be overlooked however. An interesting clinical feature might be long lasting back pain after stent implantation. The new venous stents are almost all characterized by increased radial force and crush-resistance. Own experience showed persistent lower back pain in young women after stenting, actually resembling PCS. Since PCS patients are relatively young, this may create a serious problem in the future. Stents cannot readily be removed and it's not unlikely that a patient has to endure a stent for more than 40 years. However, this entity has not been clearly depicted in the literature yet. Until we receive reliable data from clinical trials, personal experience may be the only deciding factor. Nevertheless, with lacking evidence and multiple unknowns, the indication for stenting should be convincing and a less aggressive strategy may be sensible for now.

Post stenting medical therapy. The data on antithrombotic medical therapy after stenting is extremely scarce. Historically, vitamin K-antagonists have been primarily suggested. In recent years, a definite transition has been made towards direct-acting oral anticoagulants (DOAC). There are also physicians that prefer antiplatelet therapy or a combination of both. The duration of antithrombotic therapy is as uncertain as is the choice of medication. After stenting an iliac vein compression, mostly a 6-months medical therapy has been suggested. A recent publication shed little more light on this subject showing no difference between a DOAC and a vitamin K-antagonist after iliofemoral stenting after deep venous thrombosis.[87] Obviously, more and larger studies are necessary to determine the optimal therapy choice and duration.

In conclusion, in a patient diagnosis with PCS a hemodynamic relevant LRV and iliac vein stenosis should at least be ruled out. If a stenosis is suspected then the hemodynamic consequences should be evaluated with angiography. When the central vein obstruction is identified as the most likely cause of the PCS, stenting of the relevant lesion is recommended with self-expandable stents. The technique of stenting has not been established yet although most aspects of the procedure are generally accepted. The most probable and feared complication is stent migration. Besides that, stenting of iliac vein stenosis more than renal vein stenosis has proven relatively safe and effective.

6. Outcome of treatment

6.1 Effectiveness of treatment

Treatment of PCS can be broadly divided into three forms of therapy: medical treatment, removal of the female reproductive organs and alteration of venous flow. While the former two have been proposed in the past, they do not appear to be very effective. Alteration in venous flow through coiling, vein transpositions and stenting are gaining interest and shows promising results.

Medical therapy. Hormonal suppression of ovarian activity has been investigated as PCS usually only occurs in premenopausal women, suggesting a hormonal influence. Several studies have investigated the effect of progestogens on complaints. Reginald *et al.*[61] have demonstrated a 75% reduction in pain on a VAS after 6 months of medroxyprogesterone (MPA) 30 mg daily. However, they did not have a control group and this effect was only found in patients with changes on venography. Patients without reduction on their venography score demonstrated only 29% decrease in VAS. Shokeir *et al.*[62] compared subcutaneous etonogestrel for 12 months with no treatment in an RCT. VAS decreased from 7.7 to 2.4 in the treatment group, compared with a change of 7.9 to 7.6 in the control group, $P<0.05$). Control patients did not receive a placebo subcutaneous insert though. Farquhar *et al.*[63] also evaluated the effect of psychotherapy. They performed an RCT with four treatment groups: 50 mg MPA daily for 4 months, 50 mg MPA plus six sessions of psychotherapy, placebo for 4 months, and placebo plus psychotherapy. Treatment effect was defined as 50% or more reduction in VAS. When MPA was administered 73% experienced effect of treatment compared to 33% in the two groups that used placebo ($P<0.001$). After nine months there was no overall significant effect. Soysal *et al.*[12] compared the effect of the Gonadotropin-releasing hormone (GnRH) agonist goserelin acetate with the effect of MPA in an RCT. Patients either received 30 mg MPA daily or monthly injections of 3.6 mg goserelin acetate for six months. Twelve months after cessation of treatment, patients on MPA had a mean reduction of 4.7±1.4 on a modified version of the Biberoglu and Behrman pelvic symptom score[88] compared with a reduction of 7.7±1.8 in patients with goserelin acetate ($P=0.00001$). Gangar *et al.*[64] did not find a treatment effect in a case series with a combination of goserelin acetate, estradiol valerate and MPA. However, this study suffered from numerous methodological limitations, including five drop-outs and two patients undergoing hysterectomy or oophorectomy in this already small case series of twenty patients.

Surgery of reproductive organs. In cases of failed hormonal treatment, it could be considered to perform oophorectomy as a method of ovarian suppression. Beard *et al.*[89] demonstrated a change of median VAS from 10 to 0 at one-year follow-up (P<0.001) after bilateral oophorectomy with hysterectomy. Hysterectomy tends to be performed to prevent withdrawal bleeding due to hormonal replacement therapy. Only one out of the 37 patients in this case series experienced little improvement. Level of evidence is poor, given the lack of a control group. Chung *et al.*[65] did perform an RCT in which they compared hysterectomy with unilateral salpingo-oopherectomy (USO) or bilateral oopherectmy (BSO) with ovarian vein embolization. The group undergoing hysterectomy with BSO demonstrated a change in VAS from 7.7 to 4.6 (P<0.05). The group with USO did not demonstrate a significant decrease in VAS (7.8 to 5.6, P>0.05). Patients with ovarian vein embolization experienced better results. While this RCT was not able to demonstrate benefit from surgery, it should be noted that this study also did not include a control group. Furthermore, the inclusion and randomization process was not transparent.

Treatment by compression therapy. Gavrilov *et al.*[90] investigated the effect of compression therapy on pelvic congestion. Patients were divided in different groups. Two were relevant for the purpose of this paper: patients with symptoms of pelvic congestion and CPP without lower limb varicosities, and patients with symptoms of pelvic congestion and without lower limb varicosities on ultrasound. The first group was treated with compression shorts class II from the upper third of the thigh, whereas the second was treated with lower limb compression stockings class II. In the first group 81% patients experienced improvement of complaints. The severity of pain on a modified pain scale decreased from 6.5±2.6 to 1.1±0.14 (P<0.05). Patients in the latter group did not experience relieve of pelvic complaints (6.27±1.33 before, 6.24±1.2 after, P=0.05). They also performed radionuclide venography during which they calculated a coefficient of PCS (Cpcs), which was the ratio of impulses counted from the parametrial veins to the impulses counted on the common iliac vein. This was performed to assess the effect of compression therapy on pelvic hemodynamics. The Cpcs decreased from 1.73±0.32 to 1.12±0.27 (P<0.05) in the first group and did not change in the latter. It should be noted that the selection process was not very transparent and that there was no randomization. Follow-up was only 14 days, so there is no information on long-term effect.

Treatment of ovarian and iliac vein incompetence. The study by Chung *et al.*[65] showed that patients experienced a significant decrease in VAS from 7.8 to 3.2 (P<0.05) after ovarian vein embolization. It is noteworthy that patients were less likely to show improvement if they scored high on a revised social readjustment scale, indicating that stress levels were of influence.

Various retrospective case series were published on this subject, none of which described a control group.[1, 9, 11-32] The largest group consisted of 202 patients. Laborda *et al.*[55] coiled the left ovarian vein in 100%, the right ovarian vein in 95.5%, the left internal iliac vein (IIV) in 91.1% and the right IIV in 73.8% of patients. After 5 years, mean VAS decreased from 7.34±0.7 to 0.78±1.2 (P<0.0001). Mean time until clinical improvement was shorter in patients with severe pain (13.5±1.9 months in patients with VAS 8-10 and 9.1±1.1 months in patients with VAS 5-7, P=0.001). All patients were initially referred for lower limb varicosities and were included based on venography results in combination with symptomatology as opposed to the Beard criteria.[7] Eleven percent were lost from follow-up.

Nasser *et al.*[91] reported similar results in a case series of 113 women (VAS decreased from 7.34±0.07 to 0.47±0.05 after 1 year, P<0.001). Embolization was performed in 97% of left ovarian veins, 64% of right ovarian veins, 80% of left IIVs and 46% of right IIVs. Patients with urgency complaints (OR 5.9 [95% CI: 1.5-23.4]) and lower limb symptoms (OR 5.3 [95% CI: 1.4-20.4]) were less likely to experience complete resolution of symptoms. Patients were included if they experienced pelvic pain for at least 6 months, in combination with tenderness at the ovarian point, and if venography uncovered ovarian vein or IIV incompetence. Twelve percent were lost to follow-up.

Kim *et al.*[17] described a case series of 127 patients in which 16% underwent unilateral and 84% bilateral ovarian vein embolization with concomitant injection of foam sclerosant. In 85% of patients IIV embolization was performed four to six weeks after initial treatment. At a mean follow-up of 45±18 months VAS significantly decreased for overall pain (7.6±1.8 to 2.9±2.8, P<0.00001), dyspareunia (3.3±3.7 to 1.5±2.7, P<0.00001) and menstrual pain (4.9±4.2 to 2.2±3.1, P<0.00001). In 5% of cases recurrence was observed. Patients were selected if PCS was suspected based on symptomatology, though the selection process was not transparent. Several smaller studies have yielded similar results.[58, 83, 84, 87, 91-97]

Treatment of renal vein compression. Pelvic congestion can also be caused by the Nutcracker syndrome: compression of the left renal vein as a result of entrapment between the superior mesenteric artery and the aorta.[78-80, 85]

D'Archambeau *et al.*[35] reported on ovarian vein embolization in 48 patients. In 40 (83%) patients compression of the left renal vein was also present. This compression was not treated. However, results were similar compared to other studies treating ovarian vein incompetence by embolization. Results should be interpreted with caution as VAS scores, including preoperative scores, were obtained retrospectively at an unknown point after treatment. No information with respect to renal function was reported. Hartung *et al.*[48, 74] reported on five patients treated by stenting of the left renal vein using a Wall stent (Boston Scientific-Schneider, Minneapolis, MN, USA). The first patient experienced stent migration with a 20 mm stent. This patient was stented again with a 16mm stent, which was also used in all subsequent patients. Two patients experienced complete relieve of symptoms (4.2- and 26.5-months follow-up), one patient experienced a different type of pelvic pain and underwent hysterectomy for endometriosis, and two patients suffered from recurrence of symptoms at 3 and 4 months after initial treatment. In both patients, minor stent migration was observed, leading to recurrence of left renal vein compression. Patients were treated based on symptoms; a confirmation of left renal vein compression on duplex, CT and venography; and after exclusion of other pathology during diagnostic laparoscopy. White *et al.*[98] investigated left ovarian vein to left external iliac vein transposition as a treatment for pelvic congestion caused by left renal vein compression. They reported on three patients who all underwent extensive examinations, including diagnostic laparoscopy to exclude other pathology. All patients experienced complete relief of symptoms one year after surgery and all three grafts were still patent. Left renal vein transposition has also been investigated in the past, demonstrating fair results in a case series of eight patients. However, this has been investigated with reference to hematuria and proteinuria as a result of left renal vein compression, rather than PCS.[99]

Treatment of iliac vein compression. Another possible cause of PCS is compression of the iliac veins. Daugherty *et al.*[85] published a retrospective case series on eighteen patients who underwent left iliac vein stenting for pelvic complaints. Median venous clinical severity score improved from 7 (range 0-10) to 3.5 (range 0-9) after a median follow-up of 11 months (range 1-59). No statistical analysis was performed. Patients were included if they suffered from pelvic pain affecting their quality of life and if non-thrombotic iliac vein compression was observed on IVUS and venography. If lower limb complaints were worse than pelvic complaints, patients were excluded. In seven cases ovarian vein incompetence was found, of which only one was treated. Treatment of iliac vein compression by stenting has been extensively investigated in association with lower limb complaints demonstrating good clinical results with excellent patency rates.[65, 90-93, 100-102] Nonetheless, no RCTs have been performed.

6.2 Complications of treatment

Complications rate is an important component for evaluation of outcomes for each treatment method. Treatment options of PCS include medical therapy, surgical and endovascular procedures.

Medical therapy consists of symptomatic pain relief treatment (analgesics, anti-inflammatory drugs, psychotherapy, etc.), hormonal therapy (danazol, medroxyprogesterone, gonadotropin-releasing hormone agonists — goserelin acetate, implanon, etc.) and venoactive drugs (micronized purified flavonoid fraction). As pain relief treatment is only episodic, evaluation of complications is not significant. Side effects of hormonal therapy include weight gain, bloating, symptoms of menopause[12] and, also, inability to use certain medication for a long-term course due to the risk of osteoporosis.[65] Usage of venoactive drugs particularly micronized purified flavonoid fraction (MPFF) for the treatment of PCS shown same effectiveness as hormonal therapy, but without significant side effects, and, therefore, are the most perspective option for the conservative treatment of PCS.[13, 14, 66, 67]

Surgical procedures are more invasive and require a general anesthetic and a longer recovery period. Given that surgical ligation can only interrupt the refluxing pathway at only limited number of locations, recurrences may be more common as well for reflux disease, other treatment options include open or laparoscopic surgery to ligate the insufficient veins. However, these procedures are rarely performed as they are more invasive than endovascular embolization.

Treatment of choice for PCS is pelvic vein embolization. Complications after this kind of treatment are rare, but may be developing during the procedure, in early or late postprocedural period. Importance of each incident must be evaluated by the type and severity of complication.

Access site complications such as bleeding, hematoma, AV fistula, are very rare and practically do not need additional therapy in comparison with complicated arterial puncture. However, Laborda *et al.*[55] reported groin hematoma in 3% of cases after pelvic vein embolization via femoral access. Lopez *et al.*[103] reported pneumothorax as a possible complication in case of jugular access. According

to recent systematic reviews, technical success of pelvic vein embolization is 96-100% (Mahmoud *et al*.,[104] Daniels *et al.*,[105] Hansrani *et al.*[106]). The main reasons for technical failure are posthrombotic changes or congenital anomalies of pelvic veins. Another important intra-procedural complication is embolization of non-target vessel, which may be caused by incorrect coil deployment or coil protrusion. Lopez *et al.*[65] presented cases of coil misplacement *e.g.* left ovarian vein coils extending into the left renal vein, and obturator or circumflex coils protruding into the left external iliac or common femoral vein. A possible reason of coil misplacement could be incorrect evaluation of pelvic vein diameter due to vasospasm.[107]

The most important complication in the early postembolization period is coil migration. Several authors presented different number of incidence: Verbrux *et al.*[60] — in 3.6% of cases, Creton *et al.*[108] — 4.2%, Laborda *et al.*[55] — 2%. Retrospective evaluation of studies shows, that during the last decade the incidence of this complication has been reduced from 4.2% to 1.6%, which likely is the result of increased experience and more active usage of detachable coils. In cases of coil migration coils most often migrate to the pulmonary circulation and very rarely to the left cardiac ventricle. In the majority of cases after coil migration patients are asymptomatic and no additional therapy is needed. Some authors presented successful cases were the coils were snared and retracted from the pulmonary artery.[56, 100] Maleux *et al.*[109] presented transient cardiac arrhythmias caused by glue migration in 8% of cases.[109] In approximately 20% of cases postembolization syndrome occurs (abdominal/low back pain, sub-febrile temperature, nausea, bloating, etc.), which usually self-limiting and can be symptomatically treated using nonsteroidal anti-inflammatory drugs. Also, an allergic reaction to medication, contrast material or coiling agent can occur. Thrombosis of varicose veins of pelvic origin is not rare but it is debatable whether this should be considered a complication.

Main late postprocedural side effect is the recurrence rate, which approximately 5%.[17, 58, 95, 101, 102] There is no evidence that reproductive function is affected. Kim *et al.*[17] not find any significant changes in follicle stimulating hormone (FSH), luteinizing hormone (LH), or estradiol levels. They reported a 50% pregnancy rate in premenopausal women.

7. Summary

7.1 PCS is an often overlooked and untreated condition with chronic symptoms which may include pelvic pain, perineal heaviness, urgency of nicturation 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.

7.2 Ovarian vein dilatation is seen in 10% of women, up to 60% of whom may develop PCS. 30% of patients with CPP as the sole cause of their pain and an additional 15% have PCS along with another pelvic pathology. However, ovarian vein diameter does not correlate well with ovarian vein insufficiency.

7.3 Etiology of PCS is multifactorial which include mechanical (congenital or acquired), hormonal and psychosomatic risk-factors.

7.4 Venous hypertension is a leading factor in development of PCS which is a result of abnormal venous flow, particularly with centrifugal/retrograde direction which leads to pelvic varices due to reflux in the ovarian or internal iliac vein, or centripetal/antegrade pathological flow, which is induced by deficiency of pelvic vein outflow, caused by intraluminal (thrombotic) or extraluminal (compressive) factors.

7.5 The structural changes of pelvic varicosities are similar to those in varicose veins elsewhere, including fibrosis of the tunica intima and media, muscular hypertrophy and proliferation of capillary endothelium. Women with PCS tended to have a larger uterus and more cystic changes in ovaries than healthy women.

7.6 Non-cyclical pelvic pain, which can be exacerbated by postural changes, walking and sexual intercourse and, also, during menstruation is main clinical symptom of PCS. Other clinical manifestations of PCS are various and can be of gynecological (dysmenorrhea, vaginal discharge), urological (disuria, urinary frequency) and, gastroenterological (nausea, bloating, abdominal cramps, rectal discomfort) nature. The main clinical sign is the presence of varicose veins on perineal, vulval, gluteal or posterior thigh areas.

7.7 Transabdominal ultrasound can exclude intrinsic pelvic conditions, demonstrate pelvic varicosities, and suggest ovarian vein insufficiency. Transabdominal ultrasound has a great diagnostic value due to direct visualization of the left ovarian vein. An ovarian vein diameter of 6 mm on transabdominal ultrasonography has been reported to have a 96% positive-predictive value for pelvic varices. Although diameter measurements alone do not correlate well with ovarian vein reflux and so the examination should also look for reflux with the patient in a 45-degree position.

7.8 Transvaginal ultrasound offers better visualization of the pelvic venous plexus compared to transabdominal

ultrasound. However its accuracy has not been validated by venography in all cases and it cannot evaluate the renal and iliac veins The presence of circular or linear venous structures with a diameter greater than 5 mm is indicative of pelvic varicosities. Reversed caudal blood flow may be seen in the ovarian veins and dilated arcuate veins may be seen crossing the myometrium.

7.9 Duplex-ultrasonography of the veins of lower extremities are a necessary part of the imaging protocol in diagnosing PCS, especially in the presence of atypical (perineal, vulval, gluteal or posterior thigh) varicose veins.

7.10 Cross-sectional CT does not have a routine place in diagnosing PCS as it does not supply information on hemodynamic changes in pelvic veins. This method has the capability to exclude other pelvic pathologies, however, could be used to identify compression of the left renal vein or iliac veins.

7.11 On MRV pelvic varicosities can be suspected as enlarged tortuous tubular structures in the trajectory of the ovarian veins, around the adnexa, and in the pelvic floor. Also, the renal veins can be assessed for signs of compression (Nutcracker syndrome), as well as the common and/or external iliac vein.

7.12 Catheter-directed retrograde selective venography of ovarian and internal iliac veins is the method of choice for the diagnosis of pelvic venous pathology. Diagnostic criteria for PCS are as following: 1) an ovarian vein diameter more than 6 mm with proven reflux; 2) contrast retention more than 20 seconds; 3) congestion of the pelvic venous plexus and/or opacification of the ipsilateral (or contralateral) internal iliac vein, or 4) filling of vulvovaginal and thigh varicosities.

7.13 Usage of IVUS in diagnosing PCS is very rare and mostly only performed when trying to detect compressive syndromes (Nutcracker, May-Thurner).

7.14 The sensitivity of laparoscopy in diagnosis of PCS is approximately 40%. Diagnostic findings during laparoscopy include existence of prominent enlarged broad ligament veins and may reveal pelvic varices. This should thus not be routinely used.

7.15 Other pathologies of the pelvis, such as: fibroids, adenomyosis, endometriosis, pelvic inflammatory disease, ovarian and fallopian tube diseases, pelvic tumors, cystitis, inflammatory bowel diseases and adhesions, pelvic arterial-venous malformations, portal hypertension, etc., should be excluded before making the diagnosis PCS.

7.16 Unfortunately, there are no universal, well-known classifications of PCS. The development of a discriminative tool, like CEAP, for pelvic venous disorders is needed to allow grouping of similar patients for the purposes of clinical decision making as well as to ensure homogenous patient populations in research studies.[110]

7.17 Symptomatic (pain-relief) therapy include analgesics, nonsteroidal anti-inflammatory drugs, psychotropic drugs, but the effect of such therapy is transient.

7.18 Hormonal therapy (medoxyprogesterone acetate MPA, gonadotropin-releasing hormone GnRH) seems to have therapeutic effect, but long-term usage is not recommended because of the high risk of osteoporosis.

7.19 Early enhancement of venous tone with MPFF may restore pelvic circulation for patients with PCS; by relieving pelvic symptoms, such as pain and heaviness, MPFF represents therefore an option for these patients.

7.20 Current surgical treatment includes open or laparoscopic surgery to ligate the insufficient veins. However, these procedures are rarely performed as they are more invasive than endovascular embolization procedures, and require a general anesthetic and a longer recovery period. Surgery of the reproductive organs is not advised as a treatment option.

7.21 injecting foam or liquid sclerosant could be used for occlusion of truncal (gonadal) veins and for the treatment of atypical varicose veins of perineal, vulval, gluteal or posterior thigh localization.

7.22 Transcatheter embolization therapy is the method of choice for the treatment of PCS. 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 will be the gonadal axes, pelvic varicose veins and insufficient tributary branches of the internal iliac veins. However, published evidence of its effect has been criticized for the lack of validated clinical and imaging criteria for the disorders responsible for pelvic venous disease.

7.23 The international acceptance of unambiguous diagnostic criteria for PCS would help in clinical practice as well as in selecting homogenous populations for clinical research.[110]

7.24 Venous compressive syndromes could also lead to pelvic venous plexus hypertension and result in PCS. Stenting the common iliac vein or left renal vein could be a good treatment option. However, randomized controlled trials assessing the effect of stenting are needed. Care must be taken not to over diagnose nut-cracker syndrome as the "pseudo-nut-cracker" appearance can show renal vein narrowing due to blood being stolen away by an incompetent ovarian vein.

7.25 Treatment of choice for PCS currently is pelvic vein embolization, in the absence of obstructions. Serious

complications after this kind of treatment are very rare.

7.26 Future communications should focus on how to properly identify PCS, as diagnosing the presence of it is not well established. They should contain a good clinical scoring system and standardized diagnostic information about the ovarian and IIV incompetence and diameter and obstructive iliac vein and renal vein lesions.

7.27 Many gaps diagnosis and treatment of PCS remain. Randomized controlled trials yielding stronger evidence for specific treatment modalities in homogenous well-defined patient populations is warranted. Since pelvic venous disorders result primarily in quality of life affecting symptoms, the primary outcome measures in these trials should be disease specific health related quality of life tools that capture the full physical, psychological and social burden of these disorders on women, and not just the effects of pain. It is necessary to develop the disease specific QOL as well as the discriminative tool to allow for accurate assessments of the effect of treatment.[110]

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