STANDARDS OF PRACTICE

Research Priorities in Pelvic Venous Disorders in Women: Recommendations from a Multidisciplinary Research Consensus Panel

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ABSTRACT

Pelvic venous disorders (PeVDs) in women can present with chronic pelvic pain, lower-extremity and vulvar varicosities, lower-extremity swelling and pain, and left-flank pain and hematuria. Multiple evidence gaps exist related to PeVDs with the consequence that nonvascular specialists rarely consider the diagnosis. Recognizing this, the Society of Interventional Radiology Foundation funded a Research Consensus Panel to prioritize a research agenda to address these gaps. This paper presents the proceedings and recommendations from that Panel.

ABBREVIATIONS

CPP = chronic pelvic pain, PeVD = pelvic venous disorder

Pelvic venous disorders (PeVDs) in women can present with a spectrum of interrelated symptoms and signs that include chronic pelvic pain (CPP) as well as lower-extremity and vulvar varicose veins, lower-extremity swelling and pain, and left-flank pain and hematuria. Historically, these different clinical presentations have been independently described as an unrelated group of "syndromes" (pelvic congestion, May-Thurner, and nutcracker) that refer to specific anatomic aberrations but fail to completely account for the underlying pathophysiology and overlapping spectrum of symptoms and signs.

A variety of imaging techniques are used to document pelvic venous reflux; however, variable and poorly validated diagnostic criteria are used (1–3). Although case series and 1 randomized trial suggest that women with CPP caused by ovarian and or internal iliac reflux benefit from embolization, the overall quality of the evidence is low (4–6). In addition, the recent appreciation that venous obstruction can cause PeVD has exposed additional gaps in our understanding of the relative importance of reflux and obstruction and their optimal management (7–9).

Although some gynecologists will consider PeVD in selected situations, skepticism about its relationship to CPP is prevalent (1,10). Consequently, only a minority of potentially affected patients are evaluated for venous disease (1). Treatment exclusions in insurance policies in the United States frequently limit access to reimbursed care in women with documented PeVD. Given the lack of broadly accepted methods to evaluate and diagnose women, the potential that some women are being treated inappropriately with the use of pelvic venous interventions is also concerning.

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In recognition of the many unanswered questions regarding PeVD in women, the Society of Interventional Radiology Foundation (SIRF) funded a Research Consensus Panel (RCP) with the goal to convene a multidisciplinary group of experts to review the current PeVD literature and develop a prioritized research agenda to address identified evidence gaps.

METHODS

In consultation with SIRF leadership, the RCP facilitator assembled an 11-member multidisciplinary panel that included representatives solicited from medical societies with a shared interest in CPP and pelvic-derived lower-extremity varicose veins in women. The assembled panel was composed of 3 gynecologists, 4 interventional radiologists, 2 vascular surgeons, and a health outcomes scientist, all with significant academic or clinical experience with PeVD. In addition, a former medical director of a large health care insurer was also included on the panel. The voting members and their nominating societies are listed in the **Table**. An audience including patients, other providers, and representatives from insurance carriers, the National Institutes of Health, the Food and Drug Administration (FDA), and industry was also invited to participate.

The 1-day panel was convened on October 8, 2017. The first session included a series of expert presentations to review the available evidence and identify gaps. This was followed by discussions to further define the critical research questions that needed to be addressed.

The facilitator then used a modification of the nominal group approach to develop consensus (11) with the use of an electronic online voting program (12). This software uses a modified Borda count algorithm in which voters rank items in order of preference. The Borda algorithm determines the ranking of each vote by giving each item a number of points corresponding to the number of items ranked lower on each voter's ballot. The item with the most cumulative points from all voters is the highest ranked of each round, with the next highest ranked items identified based on their cumulative points in decreasing order. A Borda count vote is considered to be better at achieving consensus than algorithms that favor simple majorities because it places more emphasis on the value ascribed by voters to all items, including those lower in their prioritized lists.

The RCP facilitator compiled a list of 16 research ideas that were typed into the online consensus rank tool Forcerank.it and shared on a projected screen for discussion and rewording by the panel when appropriate. An online link to the Forcerank.it list was e-mailed to each panelist, who were each given a few minutes to privately rank the research ideas based on priority. After staff confirmed that all responses had been submitted, Forcerank.it compiled the panel's preliminary rankings, which were shared with the panel on a projected screen for discussion. Subsequently, the top 6 items were reprioritized by means of the same process, developing the final consensus recommendation of the panel.

With the editorial support of the entire panel, the facilitator prepared this summary of the proceedings after performing Pubmed searches to ensure that the most up-to-date references were included. Because this project did not involve review of any protected health information, the work did not require Investigational Review Board endorsement.

Since the October 2017 panel meeting, progress has been made on the proposed agenda. In late July 2018, a multidisciplinary international work group had a 1-day face-to-face meeting and developed a PeVD discriminative instrument by consensus. Another work group was awarded a grant in July 2018 from SIRF for developing PeVD quality-of-life (QOL) instruments.

Table 1. Panelists and Their Affiliations

RCP Facilitator	Society Affiliation
Neil Khilnani, MD FSIR, FAVLS	SIR
Voting Panel	
Jane Daniels, PhD	Professor of Clinical Trials (Nottingham, United Kingdom)
Kathleen Gibson, MD FACS, FAVLS	AVLS
Lee Learman, MD, PhD, FACOG	ACOG
Lindsay Machan, MD, FSIR	SIR
Richard Marvel, FACOG	IPPS
Mark Meissner, MD, FACS, FAVLS	AVF
Susan Nezda, MD, MBA, FACEP	Healthcare consultant and former Chief Medical Officer for CMS, Region V
Melvin Rosenblatt, MD, FAVLS	AVLS
Frank Tu, MD, MPH, FACOG, FACS	IPPS (via conference call)
Ronald Winokur, MD RPVI	SIR
Sarah White, MD, MS, FSIR	SIR Foundation
Anthony Venbrux, MD, FSIR	SIR

Note–The RCP Facilitator solicited the nominations of the representatives from the ACOG, AVLS, formally the ACP, the AVF, and the IPPS to join the SIR and SIR Foundation appointed representatives on the panel.
ACOG = American College of Obstetricians and Gynecologists; ACP = American College of Phlebology; AVF = American Venous Forum; AVLS = American Vein and Lymphatic Society; CMS = Centers for Medicare and Medicaid Services; IPPS = International Pelvic Pain Society; RCP = Research Consensus Panel.

SUMMARY OF PANEL PRESENTATIONS

Chronic Pelvic Pain in Women—Prevalence, Impact, Evaluation, Differential Diagnosis, and an Introduction to Management

To create a consistent working definition of CPP, the American College of Obstetricians and Gynecologists proposed the following criteria for CPP: noncyclic pain lasting for at least 6 months, localized by the patient to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, lumbosacral back, or buttocks, and associated with functional disability or medical care (13,14). Although prevalence estimates vary, it is likely that 1 in 6 women of reproductive age has experienced CPP, with a 14.7% prevalence reported in the US and 24% in the UK (15–17). This prevalence is similar to that of many common health conditions, including asthma and back pain (18). Like other chronic pain conditions, CPP has a negative impact on patients, families, and society (15,16). It limits activities that are important for QOL, relationships, self-esteem, productive work, and continued employment. These symptoms often exist for many years, despite, in many cases, several unsuccessful physician encounters in an attempt to identify a cause and receive successful treatment (19). The costs of CPP and its treatment are estimated to exceed $3 billion annually in the United States (18).

CPP fits the description of chronic overlapping pain conditions (20). This paradigm emphasizes that in the majority of patients with persistent pain, more than one chronic pain condition is present, and there is usually no single pain trigger that can be treated and resolve the symptoms. Women with CPP often have one or more conditions that may, or may not, contribute to their symptomatology, including (in no particular order) endometriosis, adenomyosis, pelvic inflammatory disease, interstitial cystitis or bladder pain syndrome, migraines, irritable bowel syndrome, fibromyalgia, chronic back pain, pelvic floor tension myalgia, nerve entrapments, gastrointestinal disease, adhesions, chronic fatigue syndrome, postural hypotension syndrome, vulvodynia, and pelvic venous disease (21).

Persistent pain is hypothesized to result in neural up-regulation that promotes increased regional pain sensitivity resulting in overlapping nerve, muscle or joint pain generators (22). Anxiety and depression are very common comorbid conditions in chronic pain patients and may also contribute to the perceived pain and increase the symptom burden (23–25). In chronic overlapping pain conditions, although the primary stimulator

may be eliminated, pain and or depression may persist, explaining some of the challenges seen in treating CPP and evaluating the literature.

To maximize impact, CPP experts suggest that physicians identify all potential pain generators and develop a comprehensive plan to manage all of them concurrently. An evaluation by an experienced pelvic pain specialist can narrow the differential diagnosis, although these specialists are not common because few gynecologists have completed structured postresidency training in CPP diagnosis and management, and CPP training within residency programs is highly variable. Some CPP generators and comorbidities may be treated based on a history and physical exam, whereas others may warrant additional laboratory tests, imaging studies, specialist consultations, and, if endometriosis is suspected or an adnexal mass is present, laparoscopic evaluation and treatment. Despite noninvasive and laparoscopic evaluation, an underlying cause for CPP is not found in up to 35%–40% of women (26,27). Of note, diagnosing PeVD with the use of laparoscopy may be unreliable owing to venous collapse induced by the pneuomoperitoneum and Trendelenburg positioning (28). The inability to identify a diagnosis leaves many CPP patients and their physicians frustrated. Suggestions that their problems are psychologic alienate women, who end up seeking advice from multiple physicians or withdrawing from further evaluation despite ongoing symptoms (19,29,30). Unnecessary treatments, including surgery, also contribute to their frustration (31).

Higher baseline pain catastrophizing (the tendency to magnify, ruminate, and feel helpless about pain) (32) was associated with greater CPP severity at 1 year. Pain catastrophizing can occur in any patient, including those without mood disorders, and is treated using cognitive behavioral therapy. Central sensitization and abnormal pain processing in the central nervous system may explain the severity of perceived symptoms in women with chronic pain (33). Neuroimaging has demonstrated cortical gray matter changes in women with endometriosis and CPP compared with normal control women (22,34). Imaging has also demonstrated an increase in periaqueductal gray matter in women with endometriosis but no CPP that potentially plays a role in pain inhibition and may explain the differences in pain perception in patients with similar pathologies (22).

The optimal management of CPP frequently requires a multidisciplinary approach that may include gynecologists, urologists, gastroenterologists, physiatrists, mental health professionals, physical therapists, and other specialists tailored to specific symptoms or conditions, such as vascular interventionalists when PeVD is a suspected etiology (29). Treatment goals should focus on restoration of normal activities and improvement of QOL, because elimination of all pain symptoms may not realistic (35). A recent cohort study observed that 525 women referred to an interdisciplinary care setting had significant improvements in CPP severity, QOL, and health care utilization (36).

The ability to establish high-quality evidence-based treatment strategies for CPP is predicated on consistent definitions of disease and symptoms. Unfortunately, the current literature includes a collage of heterogeneous disease definitions and outcome measures. When such heterogeneity exists, studies looking at the same patient group can arrive at different conclusions. In addition, there are several examples of promising initial case series and nonrandomized studies suggesting treatment successes in CPP that have been followed by placebo-controlled trials demonstrating that the benefits were either nonexistent or very small in magnitude (37–40).

Pathophysiology of Pelvic Venous Disorders

When discussing the pathophysiology of PeVDs, it is useful to consider the pelvic venous circulation as composed of 4 interconnected venous systems: 1) the right and left ovarian veins; 2) the common, external and internal iliac veins; 3) the left renal vein; and (4) the superficial veins of the lower extremities (41,42). The veins of the uterus, ovaries, bladder, distal colon, and the parietal structures of the pelvis communicate, through the pelvic floor, with veins from the anterior thigh, perineum, buttock, and posterior thigh (41,43,44). Anatomically, these connections between the pelvis and lower extremity have been described as “escape points”: The inguinal (location of the round ligament escape point), obturator, pudendal and gluteal points function like perforating veins, connecting the superficial veins of the thigh with the deep veins of the pelvis (41). Reflux through these escape points can lead to vulvar and lower-extremity veins.

The pelvic veins can be further considered to include 3 venous beds (also known as reservoirs): 1) the visceral and parietal pelvic veins; 2) the left renal and perihilar veins; and 3) the superficial veins of the vulva and lower extremity. It is hypothesized that symptoms arise from nociceptor stimulation caused by venous hypertension or distension of a reservoir.

There are 4 potential clinical presentations of PeVD: 1) pelvic symptoms (typically CPP, which may be further localizable to sexual, urinary, or anorectal locations); 2) typical (saphenous distribution) and atypical (nonsaphenous distribution) pelvic-origin lower-extremity and vulvar varicosities, with or without symptoms; 3) obstructive lower-extremity varicosity symptoms (edema or exercise-induced limb pain); and 4) renal symptoms (left hematuria and/or flank pain). These manifestations result from 2 potential patterns of reflux, in the ovarian or internal iliac tributary veins, and 2 potential patterns of obstruction, in the left renal vein or the common or external iliac veins. In addition, primary obstruction of the left renal or either common iliac veins can produce secondary reflux in the left ovarian or either internal iliac veins (45).

Symptom type and location seem to depend on whether pressure is transmitted to the distal venous reservoir only (uncompensated physiology) or decompressed (compensated physiology) through reflux via collaterals. Uncompensated reflux in either or both the ovarian vein or internal iliac vein tributaries may lead to CPP. However, the exact same reflux may be decompressed through the pelvic escape points (compensated) and lead primarily to pelvic-origin lower-extremity and or vulvar varicosities, often without any significant pelvic pain. Similarly, uncompensated obstruction of the left renal vein or either common iliac vein leads to pressure transmission and symptoms referable to the left kidney or the lower extremity, respectively. Conversely, compensated obstruction of each of these veins (by reflux through the ipsilateral ovarian in the case of left renal vein obstruction or retrograde flow via the ipsilateral internal iliac veins in the case of common iliac obstruction) results in pelvic venous hypertension and pelvic varicosities or, if the escape points are also incompetent, lower-extremity and vulvar varicose veins.

Patient-Reported Outcome Instruments for Women with Chronic Pelvic Pain

No patient-reported outcome instruments (PROs) have been developed specifically for CPP, although several are worth noting. The Endometriosis Health Profile 30 assesses QOL in women with endometriosis, including pain symptoms (46). The Uterine Fibroid Symptom–QOL Scale (UFS-QOL), initially developed for use in studies of uterine fibroid embolization, is a valid and reliable PRO that has been used in studies comparing vascular and nonvascular treatments for symptomatic uterine fibroids (47–50). It includes an 8-item disease-specific symptom scale, and a 29-item health-related QOL scale comprising 6 subscales (50). None of the symptom scale items address CPP.

One could adapt the UFS-QOL by creating a symptom scale specific for CPP and retaining the QOL scale for use in CPP. However, such a tool would not be acceptable for use by the FDA trials that seek a labeling claim, because many of the items were developed based on expert rather than patient recommendations (51). To the extent that PeVD symptoms and QOL impact are different from those of CPP in general, a new CPP PRO would need to include PeVD-related items to optimize its content validity and ensure its sensitivity to change as a patient’s condition changes. Given the varied presentation of the various forms of PeVD, different disease-specific QOL instruments or dimensions of a single instrument may be required, because symptoms in patients with chronic left renal, vulvar, or lower-extremity venous disease likely affect patients differently than PeVD-derived CPP.

Imaging of Pelvic Venous Disorders

Transcatheter venography of the ovarian and internal iliac veins in the head-up position was the first pelvic venous imaging test (52–56) and is considered to be the standard approach for identification of ovarian and internal iliac vein reflux and pelvic varicosities. Catheter venography is also able to image the left renal and iliac veins as well as providing access for immediate endovascular interventions.

Unfortunately, the use of venography for diagnosing reflux is not based on formal validation studies. The literature and current practice demonstrate significant variability in how catheter venography is performed and interpreted, confounding the ability to identify truly affected and unaffected patients as well as affecting the outcome evaluations of therapy (57,58). Test-retest reliability of pelvic venography for reflux disease has also never been objectively evaluated.

Similarly, venography to evaluate for venous obstruction has not been validated. Some of the challenges of imaging obstruction is that iliac and left renal vein narrowing is evident in many asymptomatic patients with normal physiology, and that significant venous compression may occur with or without collaterals. A pressure gradient can be measured to assess the physiology; however, in patients with collaterals, the gradient across a significant renal or iliac vein obstruction may not be greater than the 3 mm Hg gradient promoted to suggest a significant lesion (59,60). However, when an elevated gradient is found, especially when it is substantially >3 mm Hg, this can serve as evidence of a significant obstruction.

Venography to diagnose nonthrombotic and postthrombotic iliac vein obstruction is being supplanted by the use of intravascular ultrasound (IVUS). IVUS is more sensitive and likely more objective and reproducible than venography in identifying venous narrowing and its severity (61). However, no high-quality evidence is available to establish IVUS criteria that would identify patients most likely to benefit from intervention for either the iliac or renal veins. IVUS provides no physiologic data, and, as noted, some element of compression is seen in many asymptomatic patients.

Transabdominal (TAUS) and transvaginal (TVUS) ultrasound are commonly used to evaluate patients with CPP, although a venous assessment is rarely included. Vascular specialists are increasingly using TAUS to examine patients suspected of having a PeVD (62,63). TAUS is inexpensive and widely available, and a combination of gray-scale, color, and duplex ultrasound has been proposed for a comprehensive assessment of the anatomy and physiology underlying most cases of PeVD (63). As most women with a PeVD are thin and consequently easy to image, TAUS is usually able to identify the periuterine venous plexus, the ovarian veins, the central internal, both common and external iliac veins, the left renal vein, and the inferior vena cava (64). Transperineal ultrasound may be a useful supplement in evaluating the pelvic escape points (63).

TVUS with Doppler has also been proposed as a primary imaging modality for PeVD (9,65). TVUS allows for identification of concurrent pelvic pathology, diameter measurement and qualitative estimate of the number of veins in the periuterine venous plexus, and assessment of flow during and after Valsalva maneuver with the use of Doppler. Because it can not evaluate the left renal, ovarian, or common iliac veins, TVUS alone can not offer a comprehensive evaluation of PeVD.

Unfortunately, high-quality evidence validating TAUS and TVUS relative to any reference standard, including venography, is not available (3,4). Furthermore, the imaging criteria for the diagnosis of PeVD are heterogeneous (3), and the terms "pelvic vein" and "ovarian vein" are frequently used interchangeably, making interpreting the literature challenging (1). Some studies have explicitly reported an ovarian vein diameter, but the threshold for what is considered to be abnormal varied considerably, from >4.5 mm to >10 mm, with >5 mm being the most frequently cited (1). In much of the literature, the vein being measured, the technique and location of the measurement, and the position of the patient during imaging were frequently not specified. Retrograde flow after release of Valsalva maneuver, continuous flow, and slow flow in the ovarian and or periuterine veins have also been also reported as criteria for an abnormal ultrasound examination, but they similarly are heterogeneously defined and not validated (3).

Ultrasound-defined diameter measurements combined with peak vein velocity ratios as a means to identify and characterize the severity of iliac and renal vein compression are used based on low-level evidence (63,66–68). Measurement of the velocity in the renal and iliac veins are susceptible to positional variability, small sample sizes in narrowed veins, and interobserver variability (69). Retrograde flow in the central internal iliac vein may suggest an ipsilateral hemodynamically significant common iliac vein obstruction, but there is no validation of TAUS compared with venography or IVUS. It has also been suggested that continuous flow in the periuterine plexus on TVUS or in the ovarian vein on TAUS indicates a common iliac or left renal vein compression, but the evidence supporting this observation is of very low quality (9).

Small studies using varied diagnostic criteria provide low-quality evidence of the value of computerized tomography (CT) and magnetic resonance (MR) in diagnosing PeVD (3). Pelvic varices can be identified and the ovarian and periuterine veins measured with the use of CT and MR in the supine position, but these modalities provide limited information on the direction and magnitude of flow (2,70). CT and MR are more expensive than ultrasound, and CT uses ionizing radiation. MR may be better at excluding alternative diagnoses than CT and ultrasound (71,72). Time-resolved contrast-enhanced MR does allow for dynamic assessment of the direction of flow in the ovarian veins (72,73). Iliac vein and left renal vein obstruction also can be imaged with CT, MR, and IVUS. At this point, there is little high-quality evidence to determine the predictive value of any of these imaging studies in identifying patients that would benefit from treatment.

Beard was the first to demonstrate an association between pelvic pain and altered venous anatomy and flow with the use of transuterine pelvic venography (TUV) (74). This less known technique uses a transcervically placed intramyometrial needle and the injection of contrast (74). A scoring system based on the ovarian vein diameter, the rate of drainage of contrast from the pelvic veins, and the diameter and tortuosity of the veins in the periuterine venous plexus was used in randomized trials to assess patients before and after endocrine therapy for CPP. Score improvement after treatment correlated well with patient response (75–77). Although not currently used by many physicians, some pelvic pain specialists occasionally use this technique to screen for venous disease at the same time as diagnostic laparoscopy (78).

There are no data regarding the test-retest reliability of any imaging study in identifying PeVD. In addition to the usual causes for variability, findings may differ at different times in the menstrual cycle, and there are no parity-adjusted criteria for abnormal studies. Venous imaging findings in patients with nonvenous causes of pelvic pain have not been studied.

A recently published systematic review of imaging for pelvic reflux concluded that the objective performance of diagnostic vascular studies relative to reference-standard catheter venography is supported by only low-quality data (3). Reasons include a lack of standardized criteria for PeVD, methodologic flaws in the studies, and diversity in the outcome parameters used in the various studies. In their review, the authors found that reversed flow direction in an ovarian vein, pelvic varicose veins >5 mm in diameter, and a vein traversing the uterine body connecting the left and right ovarian plexus were findings most likely to correlate with reflux identified on catheter venography.

Outcome of Embolization in Women with Chronic Pelvic Pain

Although surgical approaches to eliminate pelvic reflux have been described in case series (79–81), these procedures have been abandoned in favor of catheter embolization. Embolization for the treatment of pelvic venous reflux is a fluoroscopically guided percutaneous endovascular procedure that occludes the refluxing ovarian and or internal iliac vein. Many investigators now also include ablation of the associated varicose venous reservoirs in the pelvis (82,83); the rationale is that by also eliminating the hypertensive venous bed, symptoms improvement may be enhanced, as noted with the elimination of varicose veins in the in the lower extremities.

In the literature and in clinical practice, there is heterogeneity in the venographic technique used, patient position during the diagnostic imaging, the number of veins examined, and interpretation of the images, as well as in the indications for embolization, embolization technique, and number and type of veins treated in each patient (1,5,57,58). There is also substantial variability in the literature in the choice of embolic agents as well as the embolization end point (5,57).

A systematic review of the literature to assess the effectiveness of embolization in women with CPP was recently published (1,4). The search selection included 21 case series and 1 randomized trial reporting on 1,308

women. The quality and heterogeneity of the studies precluded meta-analysis, so results were tabulated and described narratively. Pain was measured on a visual analog scale (VAS) in 9 studies, though at varying time points. Early substantial relief from pain symptoms as measured with VAS was observed in ~75% of women, which generally increased over time and was sustained. Although there is a high rate of technical success with the use of embolization, a finite failure rate is defined (6%–32%) (1), which may be related in part to which vessels are examined, techniques used for venography and embolization, which and how many vessels were embolized, and how the outcomes are assessed (57,58). The conclusions of this review were aligned with those of a second systematic review published in the same year (5) and a systematic review published two years later (84).

Complications in the systematic reviews were very low, and the proportion of women who had worsening of their symptoms after embolization was < 1% (1,2,4,5,84). No effect on menstrual function has been found in retrospective reviews of the small numbers of patients who were evaluated (85,86). No prospective data are available to substantiate changes in estrogen levels after embolization, and retrospective data in small numbers of women suggest no change in ovarian function (82).

The authors of the systematic reviews cite the most significant limitations identified in the literature is the lack of generally accepted well defined clinical criteria for the diagnosis of PeVD, lack of patient-meaningful outcome measures, and absence of high-quality randomized controlled trials (RCTs) comparing treatment with placebo (1,2,4). The 1 RCT of embolization compared with hysterectomy was considered to be at risk of potential biases and deemed to be low quality (6). Using the Grading of Recommendations Assessment, Development, and Evaluation criteria, the methodologic quality of the aggregate data supporting embolization of reflux associated with PeVD is very low.

Surgical and Endovascular Options and Outcomes for Treatment for Clinically Significant Iliac and Renal Vein Compression

Although compressive lesions of the common iliac and renal veins are common on noninvasive imaging studies (87,88), most are asymptomatic and the factors associated with the development of symptoms remain poorly understood. The prevalence of pelvic or lower-extremity symptoms and varicose veins caused by compression of an iliac or left renal vein is unknown (7–9,57).

Historically, a variety of surgical procedures were used to treat nonthrombotic and postthrombotic iliac venous lesions for limb symptoms. However, these have been abandoned in favor of percutaneous endovascular iliac vein stenting. There is evidence to support stenting of thrombotic and nonthrombotic iliac vein lesions related to venous leg ulcers, leg edema, pain and venous claudication (89,90). However, even for these patients, the selection criterion is poorly defined, and the outcomes of iliac vein stenting has been evaluated in only a limited number of comparative studies (91,92). In particular, compression of the left renal vein continues to be addressed with a variety of surgical and endovascular procedures with only low-quality evidence to support each approach (93). Both surgical and endovascular methods to treat left renal vein compression are less successful than those for iliac vein stenting of nonthrombotic iliac vein compression and are associated with higher rates of morbidity (93).

Although small case series have suggested improvement of CPP after left common iliac vein stenting (7,8) and improvement of CPP, flank pain, or hematuria after renal vein surgery and stenting (9,94), the strength of the evidence is low. Given the current evidence of overuse of iliac stenting, it must be emphasized that most patients with venous compressive lesions are asymptomatic and require no treatment (92).

In women with concurrent reflux and obstruction, the criteria for which venous abnormalities should be treated are not established. Recently published systematic reviews of the embolization literature found that <1% of women treated with embolization without screening for obstruction had worsening of their symptoms (1,4,5,84), and some have argued that this is potentially at the expense of clinical benefit (57). A single-center retrospective review of women with pelvic-origin lower-extremity varicose veins or CPP who were screened for renal and pelvic vein reflux and renal and iliac vein obstruction (with the use of ultrasound criteria for obstruction that have not been robustly validated) demonstrated that embolization alone performed in women with ovarian reflux and left renal vein obstruction, without flank pain or hematuria, resulted in clinical benefit in 97%. Clinical persistence, without worsening, was noted in the remaining 3% (9).

Treatment Options for Pelvic-Origin Lower-Extremity and Vulvar Varicose Veins

PeVD can lead to varicose veins in the vulva, perineum, and posterior thigh or a typical saphenous distribution that may be associated with the entire spectrum of lower-extremity venous disease (clinical-etiologic-anatomic-pathophysiologic [CEAP] classifications 2–6). Among patients presenting with pelvic-origin lower-limb and vulvar varicosities, <10% have been reported to have pelvic symptoms (95).

In women with pelvic-origin leg and vulvar varicosities, there is controversy regarding the value of pelvic embolization and or iliac or renal vein stenting as opposed to limited direct treatment of the leg and vulvar varicosities with the use of visual-, ultrasound-, or fluoroscopy-guided sclerotherapy (95–97). In women without significant CPP, the investigators advocating limited treatment inject the "transitional" varicosities at the pelvic escape points along with treatment of varicose veins of the leg and vulva, reserving direct suprainguinal treatment for recurrent or persistent symptomatic varicose veins (44,98,99). Other investigators have reported significant rates of recurrence if the pelvic venous pathophysiology is not addressed and have advocated initial treatment of the pelvic source of reflux (100).

No RCTs or prospective studies comparing treatment strategies for pelvic-origin vulvar or limb varicosities have been published, and the current literature is limited to single-center case series (100–103). These small series have failed to demonstrate significant improvement in lower-extremity varicose veins after pelvic venous embolization or stenting, although improvements in vulvar varicose veins after pelvic embolization were noted in 1 study (104).

Gynecologic Options and Outcomes for Pelvic Venous Disorders

A recent Cochrane systematic review concluded that there are few high-quality studies for the treatment of CPP regardless of its etiology (35). Two RCTs evaluated hormonal treatment of CPP in women PeVD documented with the use of TUV, and demonstrated statistically significant improvements in pain and TUV scores in those who received methoxyprogesterone (MPA) with psychotherapy compared with placebo or MPA or psychotherapy alone (76,77). In another similarly designed RCT, goserelin proved to be more effective than MPA in decreasing pelvic symptoms and TUV scores (75). Another, open-label, RCT demonstrated significant improvements in pain and TUV scores in patients treated with a subcutaneous progestin implant of etonogestrel versus those receiving no treatment (78). These studies have been criticized because hormonal therapy is also an effective treatment for other causes of CPP, and consequently the improvement in these patients may not be related PeVD treatment despite the improvement of the TUV score. Some have also expressed concern that the improvements with hormonal therapy are not sustainable (42) and can be associated with a variety of undesirable side-effects (35,105).

Some 10%–13% of all hysterectomies are performed for CPP although the fraction performed for those related to PeVD is not known (31). As with embolization, there are no good-quality RCTs documenting the benefit of hysterectomy in patients with CPP of all causes, although what is available consistently shows pain relief in the majority of patients (106–109). However, these benefits may be confounded by other benefits of hysterectomy, they do not specifically address benefits in women with PeVD, and there is evidence that residual and recurrent symptoms occur in a reasonable number of patients (82).

There is a single RCT comparing ovarian vein embolization with hysterectomy in women with CPP refractory to MPA. Alternate diagnoses were excluded by ultrasound, CT, and laparoscopy, and catheter venography was used in to document PeVD in each patient before randomization. After treatment, embolization patients had a statistically significant greater

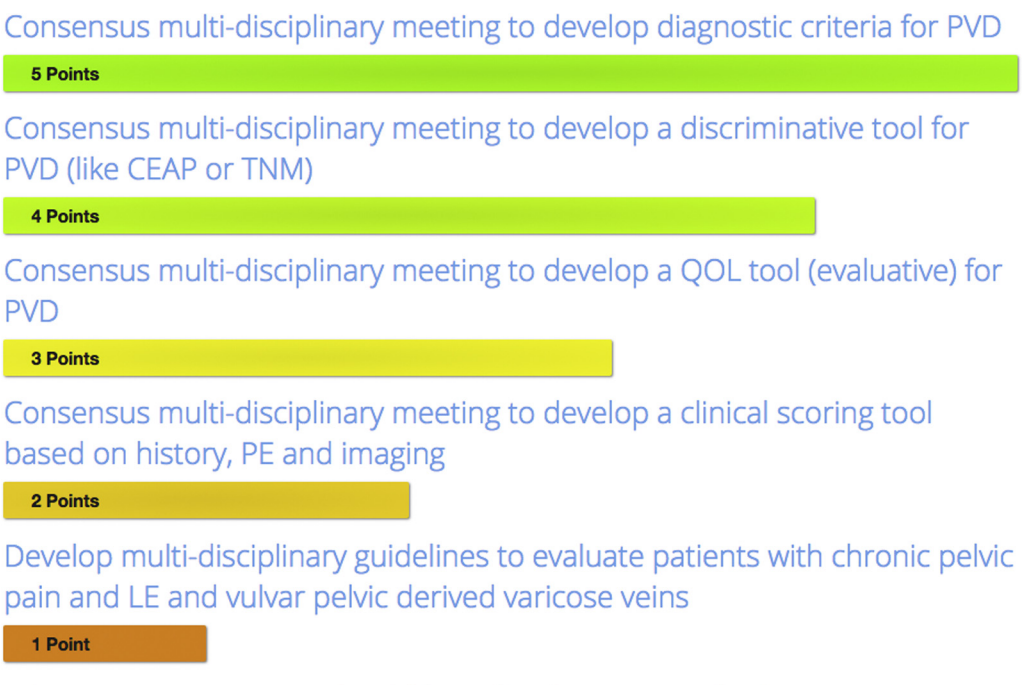

Figure. Final panel ranking of critical research questions.

decrease in mean VAS for pain than those treated with hysterectomy with bilateral or unilateral oophorectomy at each visit in the 2-year follow-up. Hysterectomy with unilateral oophorectomy was shown to decrease pain less than bilateral oophorectomy (6). However, this study has been characterized as low-quality evidence by methodologists because the patients were not blinded to their treatment and because details were missing from the manuscript, including how patients were randomized (1,4).

PANEL PRIORITIZATION AND DISCUSSION

In the discussion that occurred before the voting, the panelists consistently opined that PeVD and its treatment have not been broadly accepted owing to a lack of validated clinical and imaging criteria for the conditions and well designed RCTs of treatment options that include homogeneous study populations and a validated and consistently used set of outcome measures. The **Figure** demonstrates the panel's final ranking of the critical research questions.

The panel acknowledged that conditions that are defined by a range of symptoms such as PeVD are challenging to study. An explicit definition based on specific criteria and validated in a range of populations and settings needs to be developed by professional consensus and universally adopted. Such unambiguous diagnostic criteria for PeVD would help in its differential diagnosis in practice and in selecting patients for research evaluating the clinical and cost-effectiveness of various treatments. A clinical scoring system that incorporates a systematically performed history, physical examination, and laboratory testing combined with specific imaging criteria was supported by several of the panelists and in a recently published preliminary study (110).

The panel felt strongly that developing a discriminative instrument to categorize various forms of PeVD would facilitate clinical care and communication as well as developing homogeneous patient populations in clinical trials. Such an instrument, similar to CEAP for lower-extremity venous disease, would ideally also be created by international consensus to encourage universal application and would define populations of patients with similar presentations and natural histories. Of critical importance in the development of such instruments is that each category be precisely defined with minimal overlap between groups. Statistically, such instruments are characterized by large stable between-subject variability. By virtue of their fundamental features, such instruments are not designed to quantitatively measure severity or change over time or in response to treatment (111).

Because the principal effect of PeVD is on a patient's QOL, the panel prioritized the development of PROs, which would serve as the optimal primary outcome measure for studies evaluating a treatment's affect. PROs are evaluative instruments used to measure improvement or deterioration in response to treatment or to monitor the natural history of the disease. By design, such tools are sensitive to small changes within subjects that reflect changes in health status (111,112). Developing such an evaluative instrument in a manner that would be acceptable to the FDA as a primary end point in studies seeking approved medical labeling was a priority of the panel (51). The panel recognized that several different PROs might be needed for each clinical presentation of PeVD.

When studying CPP caused by PeVD, attention must be given to the diagnosis and management of overlapping pain conditions that are common in women with CPP. At the same time, performing a study limiting the population to patients where other comorbid conditions are eliminated leads to outcomes that are not generalizable to the chronic pelvic pain population. However, if a plan of management for other comorbid conditions is included as part of the treatment for all patients, the benefit of interventions for PeVD would be more significant. It was recommended that clinical trials should consider incorporating rather than excluding overlapping pain conditions to promote identification of safe and effective therapies for patients that can be applicable to real-world populations with chronic pelvic pain (20). The panel recognized that performing a comprehensive evaluation of CPP, especially with laparoscopy for all patients, would be costly and recommended that a gynecologist familiar with endometriosis, pelvic musculoskeletal disorders, and central sensitization participate in protocol development and evaluate all patients in CPP research studies.

The panel supported abandoning the "syndrome" nomenclature used to describe the various forms of PeVD to avoid the historical misinformation associated with those labels. The panel favored replacement with the term "pelvic venous disorders," which is inclusive of all of the clinical manifestations and underlying pathophysiology. Finally, the panel discussed the value of creating a registry of patients treated for PeVD, with the use of the to-be-developed disease definition and discriminative and clinical outcomes tools. Registries would allow collection of data that could be helpful in decision making and in planning clinical trials.

This panel did not specifically discuss the issue of PeVD in men. Gonadal vein reflux in men can lead to varicoceles, and well defined diagnostic criteria and evidence-based management guidelines already exist for that entity (113,114). The panel discussion regarding left renal vein and iliac vein obstruction in women is relevant to men with recognition that the variation in anatomy of the gonadal veins results in sex differences in how compensated left renal vein obstruction clinically presents. CPP is an important problem in men and has a different differential diagnosis (115). Although very little literature addresses this issue, PeVD can cause CPP in men. Case reports have suggested iliac obstruction as a cause of male CPP and varicocele (116), as well as pelvic-origin lower-extremity varicose veins in men caused by iliac vein reflux (44), although there is no convincing literature describing CPP or lower-limb varicose veins caused by testicular vein reflux.

CONCLUSION

A panel of experts representing several societies of physicians involved in the care of women with PeVD identified the most critical research topics related to this topic. The panel prioritized developing:

1. Consensus on the clinical and imaging criteria for PeVD.
2. A discriminative tool to categorize patients with PeVD.
3. QOL tools to measure the health burden in women affected by PeVD and its change after treatment.

The panel recommended international multidisciplinary involvement in the research agenda with the goal of gaining broad endorsement of the disease definitions and tools. Although RCT data are needed, the panel was clear that it is necessary to first develop the required research tools to ensure that the financial and time investments made to support PeVD research would yield evidence that will be broadly accepted.

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