

The relationship between pelvic vein incompetence and chronic pelvic pain in women: systematic reviews of diagnosis and treatment effectiveness

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***National Institute for
Health Research***

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Abstract

The relationship between pelvic vein incompetence and chronic pelvic pain in women: systematic reviews of diagnosis and treatment effectiveness

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Background: Pelvic congestion syndrome (PCS) is described as chronic pelvic pain (CPP) arising from dilated and refluxing pelvic veins, although the causal relationship between pelvic vein incompetence (PVI) and CPP is not established. Non-invasive screening methods such as Doppler ultrasound and magnetic resonance venography are used before confirmation by venography. Percutaneous embolisation has become the principal treatment for PCS, with high success rates often cited.

Objectives: Our proposal aimed to systematically and critically review the definitions and diagnostic criteria of PCS, the association between PVI and CPP, the accuracy of various non-invasive imaging techniques and the effectiveness of embolisation for PVI; and to identify factors associated with successful outcome. We also wished to survey clinicians and patients to assess awareness and management of PCS and gauge the enthusiasm for further research.

Data sources: A comprehensive search strategy encompassing various terms for pelvic congestion, pain, imaging techniques and embolisation was deployed in 17 bibliographic databases, including MEDLINE, EMBASE and Web of Science. There was no restriction on study design.

Methods: Methodological quality was assessed using appropriate tools. Online surveys were sent to clinicians and patients. The quality and heterogeneity generally precluded meta-analysis and so results were tabulated and described narratively.

Results: We identified six association studies, 10 studies involving ultrasound, two studies involving magnetic resonance venography, 21 case series and one poor-quality randomised trial of embolisation. There were no consistent diagnostic criteria for PCS. We found that the associations between CPP and PVI were generally fairly similar, with three of five studies with sufficient data showing statistically significant associations (odds ratios of between 31 and 117). The prevalence of PVI ranged widely, although the majority of women with PVI had CPP. Transvaginal ultrasound with Doppler and magnetic resonance venography are both useful screening methods, although the data on accuracy are limited. Early substantial relief from pain symptoms was observed in approximately 75% of women undergoing embolisation, a figure which generally increased over time and was sustained. Reintervention rates were generally low. Transient pain was a common occurrence following foam embolisation, while there was a < 2% risk of coil migration. Confidence in the embolisation technique is reasonably high, although there is a desire to strengthen the evidence base. Even among women with CPP, fewer than half had any knowledge about PCS.

Conclusions: The data supporting the diagnosis and treatment of PCS are limited and of variable methodological quality. There is some evidence to tentatively support a causative association, but it cannot be categorically stated that PVI is the cause of CPP in women with no other pathology, as the six most pertinent drew on clinically disparate populations and defined PVI inconsistently. Embolisation appears to provide symptomatic relief in the majority of women and is safe. However, the majority of included studies of embolism were relatively small case series and only the randomised controlled trial was considered at risk of potential biases. There is scope and demand for considerable further research. The question of the association of PVI and CPP requires a well-designed and well-powered case–control study, which will also provide data to derive a diagnostic standard. An adequately powered randomised trial is essential to provide evidence on the effectiveness of embolisation, but this faces methodological challenges.

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Glossary

Computed tomography A medical imaging technique using tomography created by computer processing to generate a three-dimensional internal image from a series of two-dimensional radiographic images.

Doppler or Duplex ultrasound An imaging test used here to investigate both the shape and size of a vein and the speed and flow of blood through it.

Incompetence (venous) When a vein becomes dilated and the blood flows slowly and backwards, or when a vein does not contain valves to prevent retrograde flow.

Index test The test or imaging method of which performance is being evaluated.

Magnetic resonance imaging A medical imaging technique that uses nuclear magnetic resonance to image the nuclei of atoms inside the body. It provides good contrast between the different tissues of the body and can be useful in distinguishing pelvic veins.

Meta-analysis A statistical technique used to combine the results of two or more studies and obtain a combined estimate of effect.

Negative predictive value The probability that a patient with a negative test does not have the disease or condition in question.

Positive predictive value The probability that a patient with a positive test has the disease or condition in question.

Quality of life An individual's emotional, social and physical well-being, and his or her ability to perform the ordinary tasks of living.

Receiver operating characteristic curve A graph that illustrates the trade-offs between sensitivity and specificity, which result from varying the diagnostic threshold.

Reference standard The best currently available diagnostic test(s), against which the index test is compared.

Reflux Backwards, or retrograde, blood flow.

Sclerosant The medium injected into a vein (e.g. foam or liquid) to block it.

Sclerotherapy A procedure in which an agent is injected into a vein in order to block or occlude it.

Sensitivity (of a test) The proportion of individuals classified as positive by the gold (or reference) standard who are correctly identified by the index test.

Specificity (of a test) The proportion of individuals classified as negative by the gold (or reference) standard who are correctly identified by the index test.

Venography An imaging test in which dye is injected into the patient's veins and radiographs are taken to visualise both the shape and size of a vein and the speed and flow of blood through it.

List of abbreviations

CPP	chronic pelvic pain	OV	ovarian vein
CT	computed tomography	PCS	pelvic congestion syndrome
EMBASE	Excerpta Medica Database	PPSN	Pelvic Pain Support Network
GnRH	gonadotropin-releasing hormone	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
IASP	International Association for the Study of Pain		
IIV	internal iliac vein	PVI	pelvic vein incompetence
IPD	individual patient data	QUADAS	Quality Assessment of Diagnostic Accuracy Study
MEDLINE	Medical Literature Analysis and Retrieval System Online	RCT	randomised controlled trial
MPA	medroxyprogesterone acetate	ROC	receiver operating curve
MR	magnetic resonance	SD	standard deviation
MRI	magnetic resonance imaging	TAUS	transabdominal ultrasound
NSAID	non-steroidal anti-inflammatory drug	TVUS	transvaginal ultrasound

Plain English summary

Pelvic congestion syndrome is a rare but possible cause of chronic pelvic pain in women; in particular, the pain is often described as a kind of pain felt after a long period of standing up. This is thought to be due to the veins in the pelvis becoming widened and the blood flow through them becoming slow, similar to what happens in varicose veins of the leg. These dilated veins can be seen on ultrasound, but may be missed if the test is performed while the patient is lying down. Doctors can block these problem veins to reduce pain symptoms.

However, not everyone agrees that the dilated veins cause pain. Furthermore, the vein-blocking treatment has not been compared against other treatments, and so the reported improvements in pain symptoms may be exaggerated.

Our project aimed to methodically look at all of the previous published research in the world regarding pelvic congestion syndrome. We found that pelvic congestion is not clearly defined and that many women do not know about it. We could not be sure how well ultrasound and other scans identify dilated veins, and whether or not women with dilated veins always have pain. We estimated that about 75% of women had improvements in symptoms after the vein blocking procedure.

We do not think that there is enough information to be absolutely sure that dilated pelvic veins do cause pelvic pain and that the vein-blocking procedure is a worthwhile treatment. We think that doctors should be made aware of pelvic congestion syndrome, but considerable further research is needed and would be welcomed by both doctors and patients.

Scientific summary

Background

Pelvic congestion syndrome (PCS) is described as chronic pelvic pain (CPP) arising from dilated and refluxing incompetent pelvic veins. The diagnosis is based on patient-reported symptoms, clinical examination, anatomical features and venographic findings. There are no generally accepted, well-defined clinical criteria for the diagnosis of PCS, reflecting the residual uncertainty that there is a causal relationship between pelvic vein incompetence (PVI) and CPP. PCS is predominantly observed in multiparous women of reproductive age, suggesting both a mechanical and a hormonal mechanism.

Diagnostic methods

The identification of incompetent pelvic veins is essential for the diagnosis of PCS. Non-invasive methods such as ultrasound and magnetic resonance imaging are inevitably the first line of investigation, with assessment of the blood velocity and flow pattern a crucial part of any assessment of PVI. The accuracy of these techniques for establishing PVI, compared with the gold standard of direct visualisation through selective venography, is unclear.

Treatment

Elimination of the blood flow through an incompetent vein is a recognised strategy for reducing the impact of symptoms. This can be achieved via percutaneous introduction of an embolic agent, such as a metal coil or a sclerosant, upstream of the dilated or refluxing veins. Once the incompetent vein is occluded, blood is diverted via other veins, and, in time, new vessels form in the place of the original. Pelvic vein embolisation is now widely used, and has become the principal treatment for PCS, with high success rates often cited. However, robust data on its effectiveness are lacking.

Objectives

The commissioning brief asked two questions:

1. What is the relationship between refluxing pelvic veins and pelvic pain syndromes?
2. What is the evidence that the embolisation of refluxing veins is effective in pelvic pain syndromes?

To address these questions, our proposal had the following objectives:

- To assess the terminology, **definitions** and criteria used in the description and diagnosis of PCS.
- To systematically and critically review the evidence regarding the **association** between radiological observations of incompetent pelvic veins and the symptoms of CPP.
- To estimate the diagnostic **accuracy** of various non-invasive imaging techniques, compared with venography, in a systematic review.
- To conduct a systematic review of the clinical **effectiveness** of embolisation of incompetent pelvic veins.
- To collect individual patient data (IPD) from available studies involving embolisation in order to identify factors associated with successful outcome, and perform IPD meta-analysis if possible.

- To survey the clinical practice of UK and international pain specialists and interventional radiologists with respect to the diagnosis and management of PCS, including the latter group's prior beliefs of the effectiveness of embolisation for PCS.
- To survey members of a pelvic pain support group to assess the lay awareness and understanding of PCS.
- To elicit an opinion from interventional radiologists and support group members on the desirability of a randomised controlled trial of pelvic vein embolisation.

Methods

For the systematic reviews of accuracy and effectiveness, a comprehensive search strategy was developed, and applied to databases from inception to March 2014 and September 2013, respectively. This was used in the 17 bibliographic databases including Cumulative Index to Nursing and Allied Health Literature, The Cochrane Library, Database of Abstracts of Reviews of Effects, EMBASE, Medion, MEDLINE and Web of Science. Bibliographies of all relevant primary articles and reviews were hand-searched and no language restrictions were applied during the searching phase.

Search terms for the condition included 'pelvic pain', 'pelvic congestion', 'pelvic or ovarian vein', 'incompetence' and 'reflux'; for the intervention the terms included 'treatment', 'endovascular therapy', 'interventional radiology', 'embolisation', 'sclerotherapy', 'ligation' and 'occlusion' and for imaging tests the terms included 'ultrasound', 'magnetic resonance imaging', 'computed tomography', 'angiography', 'phlebography' and 'venography'. There was no restriction on study design in either search. Identification of relevant citations for the reviews of diagnostic definitions and association used the studies identified by these searches.

All manuscripts selected for inclusion were assessed for their methodological quality using the Newcastle–Ottawa Scale for the association review, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) scale for the accuracy review and a checklist for case series, and Cochrane Risk of Bias tool for the effectiveness review.

The quality and heterogeneity generally precluded meta-analysis and so results were tabulated and described narratively. We considered that the proposed IPD meta-analysis would not yield enough comparable, high-quality data to make any sophisticated analysis worthwhile and so we did not proceed with this.

The three surveys used SurveyMonkey™ (www.surveymonkey.com; Palo Alto, CA, USA) as the platform and were provided to pain specialists attending a conference, members of the British Society of Interventional Radiology and the membership of the Pelvic Pain Support Network.

Results

Studies included in the four reviews

We identified six relevant association studies, all which had issues regarding the selection of the controls or the size of the study. In the accuracy review, 10 studies involving ultrasound and two studies of magnetic resonance venography, all compared against conventional venography, were included. Over half had issues such as partial verification bias, precluding the calculation of accuracy parameters. The effectiveness review comprised 21 case series and one poor-quality randomised trial reporting on 1308 women. We attempted to restrict the review to prospective studies in order to reduce selection bias, but in some studies it was impossible to be completely certain from the methodology that included participants were not retrospectively identified from medical records. The studies included in the accuracy and effectiveness reviews were also considered for the assessment of definitions of PCS.

Review results

There was no single, clearly defined criterion for a diagnosis that was reported in the all of studies included in the review. The majority cited pelvic pain, dilated ovarian veins and venous reflux or congestion as principal features of PCS, but many did not give thresholds or further clarification, or, where they did, these were heterogeneous.

In six case-control studies, five had useable data from women with and without CPP, where we found that the associations were generally fairly similar, with three studies showing statistically significant associations (odds ratios of between 31 and 117). The two smallest studies failed to reach statistical significance in the odds of association, perhaps because they were too small to detect a difference. The proportion of women found to have PVI who reported CPP ranged considerably, from 39% to 91%. Polycystic ovaries were observed more frequently in the group with CPP and PVI in two studies. The prevalence of PVI ranged widely, although the majority of women with PVI had CPP. Conversely, in the four studies of asymptomatic women undergoing pelvic vein imaging for other reasons, no more than half had PVI, although again the prevalence ranged widely. Where lower-limb venous insufficiency was seen, between 60% and 77% of women also had pelvic varices.

Transvaginal ultrasound (TVUS) with Doppler has a place in the screening of women for pelvic varices, although the data on its accuracy are limited. One study provided diagnostic accuracy parameters of 96% sensitivity [95% confidence interval (CI) 92% to 99%] and 100% specificity (lower 95% CI 97%), with positive and negative predictive values of 100% and 94%, respectively. Similarly, magnetic resonance venography appears to be reproducible, but accuracy data are limited to one study that suggested 88% sensitivity and 67% specificity for identifying PVI in the OV. Imaging modalities that demonstrate both venous dilatation and reflux are necessary.

In the systematic review of embolisation for PVI, approximately one-third of patients clearly had bilateral embolisation, with metal coil placement being the dominant technique. Early substantial relief from pain symptoms was observed in approximately 75% of women, a figure which generally increased over time and was sustained. Where pain was measured on a visual analogue scale, statistically significant reductions following treatment were observed in all studies. Reintervention rates were generally low. Where measured, embolisation reduced the diameter of dilated veins to a significant degree, with minimal residual reflux. There were few data on the impact on menstruation, ovarian reserve or fertility, but no concerns were noted. Transient pain was a common occurrence following foam embolisation, while there was a < 2% risk of coil migration.

Survey results

From the three surveys, a few key themes were identified, perhaps most significantly that there are some dissenting opinions regarding PCS as a cause of CPP. First of all, although pain specialists and interventional radiologists vary in their approach to diagnosis, it is obvious that surgical management does not appear to be favoured. The majority of interventional radiologists do not perform many, if any, embolisations for PVI, and although their confidence in the procedure is reasonably high, they have a desire to see the evidence base strengthened. Even among women with CPP, fewer than half had any knowledge about PCS.

Conclusions

The data supporting the diagnosis and treatment of PVI in the presence of CPP are limited and of variable quality, and considerable further high-quality research is required to thoroughly address the research question. There is some evidence to tentatively support several of the required criteria which would indicate a causative association, but it cannot be stated that PVI is the cause of CPP in women who have no other pathology, a conclusion echoed in some dissenting views among the clinical community. Transvaginal Doppler ultrasound and magnetic resonance venography are widely used and useful screening methods, but, ultimately, they cannot replace conventional venography if embolisation is planned. Embolisation appears to provide good to complete symptomatic relief in the majority of women.

Implications for health care

There exists a proportion of women for whom no cause for their pain can be found at laparoscopy; this causes anxiety for the patient, and the search for a diagnosis can be protracted, placing a significant demand on health-care resources. The strength of the evidence with respect to diagnosis and management is insufficient for any clinical recommendations to be made, but some good practice points can be listed. When taking a clinical history from a woman with CPP, gynaecologists should ask about specific pain symptoms, including whether pain is more severe after periods of standing and relieved by lying down. If this identifies incompetent pelvic veins, the radiologist can discuss the possibility of PCS as a diagnosis with her gynaecologist, highlighting the uncertainty in the data. In examining the patient, the presence of any vulval and lower-limb varicose veins should be noted. Transvaginal Doppler ultrasound should be available for women exhibiting symptoms indicative of PVI. If this identifies incompetent pelvic veins, the possibility of PCS as a diagnosis can be discussed with the patient's gynaecologist, highlighting the uncertainty in the data. If there are interventional radiologists available who perform embolisation of pelvic veins, a referral may be considered. Women should be counselled that the embolisation, although apparently safe, may not provide complete relief of symptoms.

Recommendations for research

There is scope for considerable further research, with robust methodology and of adequate size. The question of the association of PVI and CPP requires a well-powered case-control study, in which women with CPP would be matched to two or more pain-free controls, using age and/or parity to match. All women would need to provide a standardised account of their pain symptoms, their gynaecological and obstetric history, and be examined for vulval or lower-limb varicose veins, before undergoing a consistent TVUS assessment using the most modern Doppler technology. Interpretation of the ultrasound and Doppler data should be undertaken in duplicate, with readers blind to each other's assessment, to determine interobserver reliability. Ideally, a small subsample of patients should have the same ultrasound procedure performed at two time points in order to assess if timing in relation to the menstrual cycle is important, and to assess intraobserver consistency. This would provide data on the odds of PVI being associated with CPP and the reproducibility of ultrasound protocol.

This potential association study is predicated on there being a clear definition of PVI, but it will also provide data to derive the diagnostic performance of each individual criterion, in terms of the ability to discriminate PCS from pain-free controls. The potential criteria themselves should be identified by consensus among women with CPP and clinical researchers in the field. For example, if ovarian vein dilatation is considered an important observation for a diagnosis of PVI, a receiver operating curve could be produced, using various thresholds to define dilatation, and the optimum cut-off value could be obtained. Those parameters with a statistically significant difference between the CPP and pain-free groups of women would be incorporated into a logistic regression model. The regression coefficients of the best-fit model could be used to weight scores for each criterion before summation to a combined score.

A further study of women with and without CPP who were prepared to have TVUS with Doppler and conventional venography would be required to provide the threshold for the total score, in addition to reliably determining the accuracy of TVUS with Doppler, again mapping the score on a receiver operating curve to determine the cut-off value that provides the optimum clinical performance with respect to sensitivity and specificity. Finally, the scoring system would be validated in a prospective study of women with CPP to determine its accuracy. This would then provide a practical, valid tool for clinical use that would assist in the identification of women for invasive confirmatory venography and, potentially, treatment of PCS.

Assuming that a clear diagnostic standard for PCS can be obtained in this method, the issue remains of whether or not embolisation is an effective treatment. An adequately powered randomised trial is essential to provide the necessary data, but this faces methodological challenges. Pain is a subjective phenomenon and prone to measurement bias unless a placebo or sham intervention is provided. A conventional venogram would be required to verify PVI immediately prior to randomisation between a legitimate or

sham embolisation. It would be challenging to maintain the blinding of the patient during the procedure, as she would merely be under sedation, but ethical, given the necessity of blinding in reducing the risk of bias and the fact that there is a low risk of complications from venography.

Finally, an economic evaluation of the diagnostic pathway and of embolisation will provide the final evidence on whether or not the proposed management strategy is cost-effective. It would be of general benefit in the area of CPP to collect information on overall and condition-specific quality of life and on the quantity and type of health-care resources consumed by women, as there is little contemporary evidence in this field.

Study registration

This study is registered as PROSPERO CRD42012002237 and CRD42012002238.

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Chapter 1 Background

Chronic pelvic pain

Chronic pelvic pain (CPP) is a common and debilitating symptom in women of childbearing age¹ and has a negative impact on quality of life. CPP is described in many ways.² The most frequently cited definition is cyclical or non-cyclical pain in the lower abdomen or pelvis, of at least 6 months' duration and occurring continuously or intermittently, which causes functional disability or limitation in activities of daily living.³ It is a common presentation in UK primary care, with 38 out of 1000 women affected annually, a rate comparable with asthma (37/1000) and back pain (41/1000).⁴ CPP can be a condition in its own right, encompassing dyspareunia (pain during sexual intercourse), dyschezia (painful bowel motions), dysuria (painful micturition) or exacerbation of dysmenorrhoea (painful periods), but it may occur independently of these symptoms. It can also be a symptom associated with conditions such as endometriosis, adhesions⁵ and pelvic congestion syndrome (PCS),⁶ and this often makes establishing a diagnosis problematic, leading to a delay in appropriate treatment.⁷ Social, neurogenic, psychogenic and psychological factors are strongly associated with CPP. Thus, providing a tailored effective treatment can be challenging, so much so that in 60% of patients no diagnosis is made.

Taylor was the first to ascribe some symptoms of CPP to dilated pelvic veins, and to coin the term 'pelvic congestion syndrome'.^{8,9} It has since been defined in many ways, but fundamentally includes the presence of incompetent pelvic veins in the presence of CPP. Ovarian vein (OV) and internal iliac vein (IIV) dilatation, slow blood flow (also called congestion), retrograde flow and reflux are all indicators of pelvic vein incompetence (PVI). The clinical and radiological approaches to identification of PVI are key determinants of the definitions. Both visible varicose veins on the vulva or upper inner thigh and dilated OVs can be described as varices, while incompetence may be applied only to reflux around venous valves.

Pelvic congestion syndrome is a controversial diagnosis, as the causative relationship between the observation of anatomical and haemodynamic changes in the pelvis and CPP is not substantiated with robust data. Some pain specialists challenge the diagnosis of PCS, considering it an artificial label that has arisen through advances in vascular imaging. Interventional radiologists point to the improvements in symptoms achieved by the occlusion of implicated veins. Nevertheless, some estimate that pelvic congestion is the underlying aetiology in a significant proportion of patients with CPP, with estimates approaching 30%.¹⁰ Part of the debate around PCS relates to the diversity of terms, definitions and criteria used when the symptoms are described.

Clinical symptoms specific to pelvic congestion syndrome

As CPP can comprise many symptoms, there is considerable overlap between those whose pain can be attributed to organic pathologies such as endometriosis and those with pain associated with PVI. When women with PCS were compared with women with CPP due to other pathology, the former were more often multiparous, and would describe the pain as on one side of the abdomen, dull and achy with sharp exacerbations, made worse by long periods of standing and walking. Conversely, lying down relieved the symptoms. Abdominal palpation over the ovarian point and a history of post-coital ache are discriminatory factors for pelvic congestion rather than for any other causes of pelvic pain (94% sensitivity and 77% specificity).⁶ Visible, disfiguring vulval varicosities are also often present, although these are reported to temporarily occur in 2–20% of pregnancies;¹¹ there are no data on their prevalence in non-pregnant women.

Pelvic congestion syndrome is considered by many to be a condition of the reproductive years, and most women with a PCS diagnosis are pre menopausal, suggesting that female reproductive hormones may influence the condition. However, some case series of embolisation of pelvic veins report treatment on women up to 75 years of age. Many cases of pelvic varices are found incidentally during Doppler ultrasound screening of the lower limb in women with varicose veins, and vascular specialists believe that treatment is warranted to prevent a recurrence of varicose veins, irrespective of pain.

A higher level of anxiety and depression is noted in women with CPP.⁵ Pain is a significant risk factor for psychological distress, and, for women without an explanation for their pain, this will be exacerbated. A tentative physiological mechanism is that the stretching and shearing forces of refluxing blood flow on the endothelial and smooth muscle cells of the pelvic vein prompt the release of vasodilators. These include neuropeptide transmitters such as substance P and neurokinins A and B, which are integral to the neurological pathways involved in stress and the regulation of emotions.

Other distinguishing features of women with PCS, compared with controls, are larger uteruses and thicker endometria. Over half of women (56%) with PCS have been found, on ultrasound scans, to have cystic changes on their ovaries, ranging from classic polycystic patterns to clusters of 4–6 cysts,¹² but not necessarily concurrent with uterine hypertrophy. These observations suggest that ovarian dysfunction plays a role in the pathogenesis of PCS, but is not the sole factor.

Risk factors

A relationship with pregnancy was noted early. The observation that the OV capacity of a pregnant woman at term is 60 times that of a non-pregnant woman¹³ led to the presumption that this contributed to chronic distension post partum. Around one-third of women will develop venous insufficiency during their first pregnancy, with the prevalence of varicose veins rising with each successive pregnancy.¹⁴ Several mechanisms are postulated, including the increased volume of blood volume, the mechanical compression by the gravid uterus on pelvic veins and inferior vena cava and increase in progesterone that cause a reduction in venous tone. Varicose veins of the leg tend to improve in the months after delivery, but little is known about the natural history of pelvic varices.

Contradictory data exist, however, with Kim *et al.*¹⁵ reporting that 63% of participants with PVI were nulliparous, and no differences in symptomatic response between these and parous women were seen following embolisation. The landmark paper by Beard *et al.*¹⁶ found no difference in a composite measure of PVI between parous and nulliparous women. PCS in nulliparous women was attributed to disturbances of the autonomic nervous system, owing to the observation that vaginal wall blood flow increased when a woman was anxious and decreased when she was relaxed.¹⁷ This corroborated the prevailing opinion at that time that pelvic congestion symptoms were at least partially psychological. This neglected the possibility that enduring chronic pain might cause psychological symptoms such as depression and anxiety, rather than being a manifestation of them, as discussed above. Although there appears to be an excess of parous women in many cohorts studied, parity alone cannot be a determining risk factor.

Anatomy

The veins of the pelvis join the superficial venous system of the lower limbs via the pudendal, sciatic and gluteal veins and by several routes to the deep venous system. Their anatomy is very complex, particularly because of the presence of venous plexuses that vary in their extent, volume, size and communications. From these plexuses, there are three collecting systems: the IIV, the OV and rectal veins. The external iliac vein originates from the femoral vein and ultimately joins the internal equivalent to form the common iliac vein. There is a single IIV in approximately half of all women, but in 30% of the population this can be duplicated or form a plexus whereby the several internal iliac tributaries drain separately into the common iliac vein. Estimates of the incidence rates of valves range from 0% to 40%.¹⁸

There are multiple connections between the veins draining different regions of the pelvis (including the OV) and between these and the veins of the lower limb, one of the most important being via the inferior gluteal vein. This vein is large and valved but can cause significant reflux into the veins of the lower limb if these veins are incompetent. The OVs arise from the plexus within the broad ligament of the uterus and flow into the inferior vena cava on the right side and the renal vein on the left, an asymmetry which contributes to differential symptoms and varicosities. At post-mortem dissection, OV valves are absent in 15% of women on the left side and in 6% on the right side.¹⁹

Sometimes, varicose veins may be associated with reflux through vulvar varices without any relation to the saphenofemoral junction or other deep-to-superficial reflux in the lower limb. Such varices also may be associated with clinical symptoms and signs suggestive of pelvic congestion, including uterine retroversion and dyspareunia. They are more common in women who have had several pregnancies and had haemorrhoids and vulvar varicosities during and after pregnancy.²⁰

Nutcracker syndrome

One particular anatomical variant is observed when the left renal vein is compressed between the superior mesenteric artery and the aorta. This creates hypertension in the left renal vein and may lead to the development of new collateral connecting veins around the renal pelvis, but also, if it persists, it can lead to renal vein incompetence and massive reflux into the left OV and the development of OV varices.²¹ The symptoms are different from those of PCS in that pain is concentrated on the left flank, haematuria is present and images show not only pelvic and vulvar varices but an elevated pressure gradient between the left renal vein and vena cava. The condition is improved by endovascular stenting.

Pathophysiology

The cause of the dilated veins is poorly understood but is thought to be a consequence of both mechanical stresses and ovarian dysfunction.

The pelvic veins are known to dilate during pregnancy, by an estimated 60 times their normal diameter, to accommodate the increase demand on the vascular system. These changes generally regress over around 6 months, but they may persist and then become compounded by subsequent pregnancies. In pregnancy, 20% of women will develop varicose veins in the lower limbs but only one-third of these women will have vulvar varices.¹⁴ It is proposed that compression of pelvic veins by the gravid uterus against the vertebrae leads to PVI, but the complex web of veins in the pelvis allows redirection of the flow. The valves in superficial veins (perineal and labial) do not allow reflux from the pelvis, but again in pregnancy these valves too become incompetent and provoke the development of varices in the vulva, perineum and lower limbs.

Oestrogen is a potent pelvic vasodilator via nitric oxide release, smooth muscle relaxation and loss of vascular responsiveness.²² Polycystic ovaries are frequently seen in excess in women with PCS.²³ It has been observed that counteracting this with intravenous synthetic ergotamine reduced pain and improved venous flow in the pelvic veins.²⁴ Temporary down-regulation of ovarian function by medroxyprogesterone acetate (MPA), progestin or gonadotropin-releasing hormone (GnRH) agonists,^{10,25,26} (see *Treatment*), improves pain, again implicating an endocrine role in PVI. The regression of the condition after menopause corroborates this theory.

Diagnosis

The accuracy of tests used to diagnose PCS is influenced by the variation in definitions for this syndrome, and in the difference criteria that determine incompetence in pelvic veins. There is some consensus in the hierarchy in which observed pathology or structural anomalies are attributed as the cause of CPP. Most studies of PCS exclude women with demonstrable endometriosis or adhesions, among other conditions, as these are considered to be the more likely cause of pain. Laparoscopy, the current 'gold standard' for the

investigation of CPP, can only identify dilated pelvic veins in the laparoscopic field of view and cannot produce objective measures of dilatation and tortuosity.²⁷ Laparoscopy is performed in the supine position, which causes decompression of the varices simply by gravity while the pneumoinflation of the peritoneal cavity during laparoscopy may cause further venous deflation. Although it has been suggested that a swift reverse of the laparoscopy table tilt from head-down to a head-up position will result in a rapid distension of the OV if reflux is present, this may not be possible or practical in the operating theatre. Thus, laparoscopy, while playing an important role in the differential diagnosis of CPP, cannot categorically identify PVI.

Venography

Venography is the real-time imaging of veins by radiography following the injection of a contrast agent. In earlier studies, the contrast was injected 0.5–1 cm into the myometrium under fluoroscopic visualisation and the diffusion into the venous system observed by taking images at 20-second intervals thereafter. This has been universally superseded by transcatheter venography, whereby a catheter is introduced into the venous system, usually via the common femoral or jugular vein, and guided to the chosen vein. The contrast agent is injected directly and its diffusion observed in real time. Radiologists assess the venous diameter, retrograde (reversed) blood flow, the presence of redundant collateral veins between veins and the delayed or stagnant clearance of contrast at the end of injection. Venography is usually performed on the left and right OVs and left and right IIVs, but some radiologists also selectively catheterise the renal veins and the external iliac veins.

Although the venogram study does require radiation and the use of contrast, and is invasive, it has several advantages over other imaging and so is considered the definitive method of identifying PVI. The diagnostic venogram gives immediate dynamic flow information and measurements of pelvic veins with the option of tilting the patient position. Furthermore, the patient is conscious and so can be asked to perform the Valsalva manoeuvre to further delineate venous reflux. This involves asking the patient to exhale against a closed glottis, for example by pinching her nose closed. This increases the intrathoracic pressure and ultimately the venous return to the heart, increasing peripheral venous pressures. The Valsalva manoeuvre prompts a short and limited reflux in competent veins, while in incompetent veins it provokes a pronounced and long-lasting reflux. If PVI is identified, the treating interventional radiologist can immediately proceed to embolisation, if this is so desired.

Ultrasound

Ultrasound uses reflected sound waves of varying frequencies to generate images. Higher frequencies produce a higher-resolution image but do not penetrate as deeply into tissues and hence transabdominal ultrasound (TAUS) uses transducers of 3–5 MHz, while transvaginal ultrasound (TVUS), being closer to the organs, can use higher-frequency transducers and, therefore, produce a better image. Standard ultrasound can identify venous structures but, to assess blood flow, Doppler ultrasound is required. Ultrasound bounces off the blood cells in a vein, causing a change in pitch of the reflected sound waves (called the Doppler effect). If there is no blood flow, the pitch does not change. Information from the reflected sound waves is processed to provide graphs or superimposed zones on the anatomical image that represent the flow of blood by the amplitude or brightness of the image.

Conventional Doppler technique relays two aspects: the velocity of the blood flow as peaks on a timeline and power of the signal on a grey scale. Colour Doppler expresses velocity and direction together, with red peaks indicating a positive shift and blue peaks indicating a negative one, with a superimposed white image reflecting increasing speed. Power Doppler shows only the strength of the Doppler signal, with the intensity of the white image proportional to the power, and omits speed and direction from the output. This renders the position of the transducer less important but makes the image acquisition more susceptible to motion from surrounding tissues.

Conventional Doppler may be hindered by the tortuous nature of veins, preventing a reproducible placement of the gates on the image, which is not an issue with power Doppler. Vessels with very slow blood flow, as might be expected in situations where OVVs are enlarged, are at the limit of the sensitivity of colour Doppler. Power Doppler can provide excellent resolution of the vein wall, and can delineate tortuous veins, but it can also fail to distinguish venous from arterial flow. There are no comparative data for the various Doppler methods and so this review cannot make any conclusions regarding the most appropriate method, but this may be irrelevant as technology continues to improve the discriminatory power and resolution of images.

Computed tomography and magnetic resonance imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive imaging techniques. Both methods involve the body passing through an array of detectors, producing a contiguous set of cross-sectional images which can be constructed into three-dimensional images. CT involves the use of a contrast agent, which is potentially nephrotoxic, and X-rays, while MRI deploys strong magnetic forces to generate images from the resonance of water molecules. The contrast of the image can be manipulated at the processing stage, avoiding the use of a contrast agent (usually gadolinium), although the latter can be used in magnetic resonance (MR) venography by dynamic subtraction of the native and contrast-enhanced images. MR venography can produce images of a quality comparable with conventional venography. Three-dimensional T1-weighted gradient echo sequences, which can be imaged in a single breath hold, in which the varices appear hyperintense, are also an effective way of demonstrating pelvic varices with MR imaging.

The disadvantage of both CT and MRI are that they are conventionally performed with the patient in the supine position, and as with laparoscopy, pelvic varices may not be as prominent. Artefacts from metallic coils after embolisation may also limit the use of MRI for follow-up imaging, but it is likely to become the initial non-invasive investigation of choice for the diagnosis of PCS.

Treatment

On development of CPP symptoms, women will invariably self-medicate with over-the-counter analgesics. There is no rationale as to why this would be effective on undiagnosed PVI, other than for relief of mild pain, and hence women progress via their general practitioner to a referral to secondary care. A previous systematic review identified 24 treatment studies and reported improvement rates from all treatments as between 24% and 100% of participants, and a similar wide range of pain scores from visual analogue scales.²⁸

Hormonal treatment

There have been two small randomised controlled trials (RCTs) of MPA for women with diagnosis of PCS, with pain scores as an outcome. One showed that MPA showed a significant reduction in pain scores compared with placebo (50% reduction of pain from baseline in 73% vs. 33%, $n = 104$; $p < 0.0001$) at 4 months. At 9 months, this effect was sustained only with the support of psychotherapy.²⁵ In the second RCT, MPA was compared against the GnRH agonist goserelin acetate over 6 months. At 1 year after treatment, goserelin remained superior to MPA in terms of pelvic venographic improvement, improvement of sexual functioning and reduction of anxiety and depressive states as subjective measures; goserelin acetate achieved a statistically significant advantage ($p = 0.0001$) compared with MPA.¹⁰ Another very small study found a benefit from a subdermal progestogen,²⁶ but with side effects such as weight gain, acne and abnormal menstrual bleeding, which may lead to discontinuation. The orally vasoactive lofexidine hydrochloride, which was hypothesised also to impact on pain by reducing vasospasms associated with pelvic venous congestion, failed to demonstrate a benefit in a small placebo-controlled trial.²⁹

Hysterectomy

A case series of 36 women with PCS undergoing bilateral oophorectomy and hysterectomy reported that two-thirds had their pain eliminated while the remainder had some residual pain at 1 year postoperatively, but in only one woman was the pain affecting her daily life.³⁰ Conversely, Chung and Hun did not find a statistically significant reduction in pain in women who had either a bilateral or unilateral oophorectomy with a hysterectomy.³¹ The failure of hysterectomy to provide adequate relief may be due to numerous anastomoses between the ovarian and uterine veins, which, if they are inadequately resected during hysterectomy, may leave residual varices. Given the trend in other benign conditions, for example heavy menstrual bleeding,³² to avoid hysterectomy when more conservative treatments are available, hysterectomy should not be seen as a first-line treatment.

Pelvic vein ligation

Ovarian vein ligation has been performed for PVI since the late 1970s, as either a unilateral or a bilateral procedure without hysterectomy. Improvements in pelvic pain were generally seen; for example, in a 2003 study of 23 women undergoing laparoscopic ligation, 78% were pain-free at 6 months postoperatively and showed no menopausal symptoms.³³ There are no randomised trials, however, and so a relative treatment effect cannot be defined. Endovascular techniques have supplanted ligation, as they are capable of being performed under conscious sedation, are quicker and have a shorter recovery period.

Pelvic vein embolisation

The embolisation of pelvic veins is via percutaneous insertion of metal coils or sclerosants such as glue or sodium tetradecyl sulphate. The aim is to permanently occlude the outflow veins mechanically and by thrombosis, ultimately causing sclerosis of the vessel. This procedure is available worldwide and the evidence for its effectiveness will be reviewed in *Chapter 6*.

Chapter 2 Objectives

The commissioning brief asks these two questions:

1. What is the relationship between refluxing pelvic veins and pelvic pain syndromes?
2. What is the evidence that embolisation of refluxing veins is effective in pelvic pain syndromes?

To address these questions, our proposal has the following objectives:

- To assess the terminology, definitions and criteria used in the description and diagnosis of PCS.
- To systematically and critically review the evidence regarding the association between radiological observations of incompetent pelvic veins and the symptoms of CPP.
- To estimate the diagnostic accuracy of various imaging techniques, compared with venography, in a systematic review.
- To conduct a systematic review of the effectiveness of embolisation of incompetent pelvic veins.
- To collect individual patient data (IPD) from available studies involving embolisation in order to identify factors associated with successful outcome, and perform IPD meta-analysis if possible.
- To survey the clinical practice of UK and international pain specialists as well as interventional radiologists with respect to the diagnosis and management of PCS, including the latter group's prior beliefs about the effectiveness of embolisation for PCS.
- To elicit an opinion from interventional radiologists and support group members on the desirability of a RCT of pelvic vein embolisation.

In the course of the project we extended the scope of surveys to include a survey of members of a pelvic pain support group, to assess the lay awareness and understanding of PCS.

Chapter 3 Definitions of pelvic congestion syndrome

Introduction

The International Association for the Study of Pain (IASP) defines CPP as 'chronic or persistent pain perceived in structures related to the pelvis of either men or women. It is often associated with negative cognitive, behavioral, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynecological dysfunction' [this Taxonomy/statement has been reproduced with permission of the International Association for the Study of Pain® (IASP). The Taxonomy/statement may not be reproduced for any other purpose without permission].³⁴

Conditions that are largely defined by a range of symptoms are challenging to study and treat consistently. Ideally, an explicit definition based around specific criteria, and validated in a range of populations and settings, would be developed by professional consensus and universally adopted. To a large extent, this has happened in rheumatoid diseases, which share a range of overlapping conditions with CPP. The American College of Rheumatology and European League Against Rheumatism derived a classification scheme, which now encompasses a wide range of rheumatological conditions, from which epidemiological and effectiveness research now reaps benefits in terms of clarity and consistency.

The condition of PCS has long been controversial, and even the name is not universally used, with the terms 'chronic pelvic pain syndrome', 'female pelvic varicocele', 'pelvic venous incompetence', 'varicose disease of pelvic veins', 'pelvic varicosity' and 'pelvic venous congestion' all used interchangeably in the literature. The variety of descriptors reflects the nature of the condition, whereby patient-reported symptoms, clinical observations and radiological findings all intersect to describe a syndrome. The professional perspective of study authors also is evident in the descriptions of this condition, with interventional radiologists more likely to emphasise the aspects of the venous system, vascular surgeons highlighting the relationship with varicose veins and gynaecologists focusing on pain and pregnancy associations.

Pelvic congestion syndrome is a diagnosis based on patient-reported symptoms, clinical examination, anatomical features, demonstrable PVI or reflux, or a combination of these signs. There are no generally accepted, well-defined clinical criteria for the diagnosis of PCS, reflecting the residual uncertainty that there is a causal relationship between PVI and CPP.³⁵ A clear definition of terms is required to establish definitive diagnostic criteria for evaluating the clinical and cost-effectiveness of treatment of women with PCS. An unambiguous diagnostic classification should help in the differential diagnosis of PCS in clinical practice and in selecting a homogeneous patient population for research. It will facilitate communication and help in identifying subgroups of patients differing from the overall population in terms of prognosis or treatment benefit.

Therefore, this review aims to assess the uniformity of diagnostic criteria and in definitions used in the literature to select patients with PCS. Although no attempt will be made here to lay down a clear diagnostic standard, suggestions for items, criteria and scores for future discussion and validation will be made.

Methods

Separation of clinical and radiological features

As with many conditions, PCS can be defined on the basis of patient-reported symptoms, clinical observations and examination and by radiological methods. The framework for assessing the definitions of PCS will reflect this, classifying the reported criteria into pain symptoms, clinical observations, pelvic venous anatomy and PVI, the last two domains being derived from ultrasound or venographic imaging. Any criteria that preclude a definition of PCS will also be noted.

Search strategy and selection criteria

Anticipating a huge number of small descriptive studies on the radiological features of PVI and of potential treatments, we restricted our review of definitions to those studies chosen for inclusion in our reviews of non-invasive imaging technologies and of embolisation of pelvic veins in *Chapters 5* and *6*, respectively. The selection criteria are not, therefore, specific to this review; we include the studies relevant to the key questions regarding PCS and the higher-quality studies of treatment.

Data extraction

From each included study, the criteria used to define eligibility for the study, or for treatment by embolisation, were extracted verbatim by one reviewer. The definitions were sought from the methods section of each paper, as these would be the criteria applied to the study population. Any distinction between the population selected for radiological investigation and the definition of PCS or PVI was noted. The extracted text was checked by a second reviewer and summarised to attempt a consistency in phraseology and format. The first reviewer confirmed agreement with the summary and the definitions were tabulated.

Analysis

We divided selection criteria into clinical symptoms, ultrasonographic definitions, venographic definitions and exclusion criteria. Clinical symptoms were subdivided into pain symptoms and clinical observations from examination of the patient. Radiological definitions were subdivided into anatomical criteria and descriptions of reflux. Anatomical criteria included the location, diameter and/or appearance of the veins, obtained from either ultrasound or venography. Descriptions of blood flow were derived from venography or ultrasound with Doppler. Where there were explicit thresholds for inclusion in the study, for example the minimum number of all criteria needed to be present, these were captured; otherwise it was assumed that all reported criteria were required.

We aimed either to identify corresponding or contradictory signs, symptoms or observations, or to identify criteria unique to single studies. Criteria were considered to be contradictory when the item was a reason for inclusion in one article and a reason for exclusion in another. The intention was to define a consensus group of criteria or definitions across the studies, which was arbitrarily defined at 75%: if more than 75% of studies that had a definition for PCS clearly reported any criterion, that criterion would be considered important.

Results

Studies reviewed

The papers considered were those already selected for the reviews described in *Chapters 5* and *6*.

Eleven were included from the review of the diagnostic accuracy of non-invasive technique^{23,36-45} and 21 were included from the review of embolisation,^{15,31,46-64} one study was included in both reviews.⁶⁵

A summary of the inclusion criteria from the selected studies is given in *Table 1*.

TABLE 1 Summary of eligibility criteria for the accuracy and effectiveness reviews contributing to the review of definitions of PCS

Component	Accuracy review	Effectiveness review
Population	Women with CPP and/or suspicion of pelvic vein dilatation and/or incompetence	Women who had a clinical diagnosis of PCS and/or radiological diagnosis of PVI, with or without CPP
Intervention/test	Non-invasive imaging compared against a reference standard of venography	Coil embolisation or sclerotherapy of pelvic veins
Outcome	Accuracy of non-invasive imaging	Subjective assessment of pain or improvement in pain symptoms
Study design	Test accuracy studies; other studies in which both non-invasive imaging and venography were used	RCTs, prospective observational studies, case series

Pain symptoms

Of the 33 studies,^{15,23,31,36-65} 13 did not specifically define the patient population as having pelvic pain.^{23,36,37,43,45-48,53-55,61,62} These studies invariably discussed definitions of PCS in the introduction section of the report, but it was not clearly stated which pain symptoms defined eligibility for the study, or else the report described the prevalence of pain symptoms in terms of percentage of patients reporting each symptom but did not indicate whether or not any were essential. In 5 of these 12 studies,^{38,39,46-48} the study population were women referred for screening or treatment of varicose veins of the leg.

A further 12 studies described their populations as women with chronic pelvic or lower abdominal pain with no further elaboration of the nature of the symptoms required for inclusion^{15,31,38,40-42,56-59,63,64} and only three specifying 6 months as the minimum duration of symptoms.^{40,44,50} Six studies did describe particular pain symptoms;^{38,39,50-52,65} one study from 1999 selected for the diagnostic review and the remainder describing the effectiveness of embolisation, all subsequent to 2007. Of the studies that defined symptoms, six described dyspareunia or post-coital ache as a required symptom,^{38,39,49-51,66} and four listed dysmenorrhoea or pain specifically just before or during menstruation.^{49-51,65}

Of the other symptoms occasionally highlighted, only two^{50,52} mentioned the exacerbation of pain after prolonged periods of standing as a defining symptom and only Carrion Otero *et al.*³⁹ included a feeling of heaviness in the pelvis or legs in the symptomology. Pain that tracked along the site of varicose veins, particularly during menstruation, was reported as defining symptoms in two studies,^{51,65} but was not reported in the presenting characteristics in any other studies. Only two studies required their study population to have tried, and been unresponsive to, medical treatment and to have persistent severe symptoms following laparoscopy.^{30,52}

Clinical observations

Examination revealing superficial varices in the pelvic region formed part of the definition of PCS in five studies.^{38,39,46,53,65} Atypical varices in the thigh, vulval or buttock area were the most frequently described criteria,^{46,49,53,65} with no further details given regarding the size or the degree of discomfort. Three studies also accepted pelvic varices in previous pregnancies in their inclusion criteria.^{38,39,49} Only one study required ovarian point tenderness to be identified in its population.⁴⁰

Venous anatomy

Ultrasonographic or venographic description of pelvic venous anatomy was a feature of the majority of case definitions in the studies reviewed, although this was not consistently defined and the terms 'pelvic vein' and 'ovarian vein' were used interchangeably. Ten studies simply stated that their populations had pelvic varices, sometimes described as dilated or voluminous.^{38,41,47,50,52-56,65} More studies reported an OV diameter, above which the vein was considered to be dilated, but this threshold varied considerably, from > 4.5 mm⁶⁷ to > 10 mm,^{57,58} with > 5 mm being the most frequently cited.^{40,42,43,59,60} Halligan *et al.*²³

grouped patients into three ranges of pelvic vein diameter without specifying a threshold. Two studies reported an ultrasound protocol that included assessment in both a supine and a tilted or upright position, with a consequent change in the diameter as a defining criterion.^{42,54}

Venous blood flow measurement

Assessment of the flow of blood through the pelvic venous system was undertaken by Doppler ultrasound, time-resolved MR venography and conventional venography, although it was frequently unclear which methodology was used for each criterion. There are many ways to describe the observations of the venous blood flow, converging on general terms such as congestion, insufficiency and reflux. A non-descript term of congestion was used in nine studies,^{41,47,50,52–56,65} sometimes with qualifying terms such as stasis or distension, and categories of severe or moderate, but without any thresholds for such grouping. Descriptions of venous reflux were marginally better, with bidirectional or retrograde flow being indicative of reflux. The location of the reflux was precisely specified in some studies^{38,51,65} or else related reflux to changes in the Doppler signal observed during a Valsalva manoeuvre.^{37,47,53} Filling of contralateral veins or filling described as 'across the midline' were indicative of pelvic vein insufficiency in nine studies,^{31,40,43,44,49,51,58,60,61} while six referred to filling of vulvar or thigh varices as a sign of PVI.^{31,40,49,51,58,60} Velocity measurements were also a criterion, but, again, there were various criteria for abnormality, including a refilling time of < 20 seconds,³⁹ a velocity of < 3cm per second⁶⁰ or apparent stasis.⁵⁹ Only Carrion Otero *et al.* described the absence of venous valves as indicative of PVI.³⁹

Composite criteria

Several studies attempted to rationalise the various different signs, symptoms and observations by defining PCS as the presence of a certain number out of all those that the study stated as inclusion or diagnostic criteria. For example, Carrion Otero *et al.*³⁹ required at least four out of the six clinical and radiological criteria sought in the study. Creton *et al.*⁶⁵ required all venographic criteria, following clinical screening, in order to proceed to embolisation. A case-control study combined three criteria, each with a scale of severity from 1 to 3, to give a score, but did not compute a threshold on which to define a case of PCS.²³ Chung and Huh³¹ deployed a similar scoring system with four criteria, but with a threshold of ≥ 5 out of 12 as indicative of PCS. These scoring systems were similar to that first proposed by Beard *et al.*,¹⁶ which was cited in one other study.⁴⁵ Scultetus *et al.*⁵³ and Ascitutto *et al.*⁴⁹ describe four groups: group 1 with only vulval varices without PVI, group 2 with isolated incompetence of the IIV, group 3 with dilatation of the OV (although without stating what diameter constitutes abnormal) and significant insufficiency, and group 4 being those with the Nutcracker syndrome.

Exclusion criteria

Few studies explicitly stated criteria that precluded a diagnosis of PCS, or excluded women from the population. Creton *et al.*⁶⁵ stated that women with Nutcracker syndrome or who had varicose veins originating principally from connections with the femoral vein or who had low pain scores were excluded. Exclusion of women whose pain could be attributable to other pathological causes, such as endometriosis, was stated in five studies.^{31,42,52,54,60}

Discussion

Summary of main findings

There was no single, clearly defined criterion for a diagnosis that was reported in the all of studies included in the review or even cited by the arbitrarily pre-defined minimum of 75%. The majority cited pelvic pain, dilated OVs and venous reflux or congestion as principal features of PCS, but many did not give thresholds or further clarification, or, where they did, these were heterogeneous. There is a need for a globally accepted diagnostic standard for PCS, which would help to standardise clinical evaluation and facilitate comparisons of outcomes of treatment effectiveness.

Strengths and limitations of the review

The review systematically extracted diagnostic criteria from relevant papers, categorised them into predetermined groups and attempted to look for consistency. A strict policy of extracting the definition from the methods section of each report was used, to extract information pertaining to the population under study. This may have meant that inclusion criteria that could be inferred from the introductory preamble were ignored and hence the frequency was underestimated. Furthermore, the studies reviewed were a subset of all those available, selected on the basis that they had been included in two other systematic reviews. In the process of screening citations for the other reviews, the authors did not locate any publication proposing a consensus diagnostic standard. It is likely that the studies here are representative and that the identification of themes has reached data saturation, to adopt quantitative research terminology.

Conclusion

Should a defining requirement for treatment of pelvic vein reflux by embolisation include CPP? It might seem inappropriate to subject asymptomatic women to an interventional procedure, albeit one that is relatively safe and minimally invasive, in the absence of symptoms, to correct a vascular phenomenon. This might be justifiable if there was sufficient evidence that embolisation of pelvic veins could prevent or reduce the risk of recurrence of varicose veins of the leg. Over one-third of studies failed to explicitly describe a pain symptom as an inclusion criterion, but this may be because authors consider CPP to be a *de facto* component in their definition of PCS, or else the study had a radiological focus and included women already screened for pain symptoms by gynaecologists.

As pain is a subjective and diverse experience, defining precisely what the threshold should be for further investigation, treatment or research is challenging. Aspects encompass location, duration, intensity, association with other events (e.g. sexual intercourse or menstruation) and response to treatment, and all could feature in any definition. A review of over 100 epidemiological studies found that the two most basic aspects of CPP, namely duration and location, were inconsistently defined.²

A minimum duration of pain of 6 months of pain is a common definition for CPP, and this could be included in any definition of PCS. Self-report of the duration of pain symptoms has the advantage that it can be captured from any population and is applicable irrespective of any prior interventions in primary care; however, this method suffers from recall bias and difficulty knowing from which point to commence the time scale. Taking the starting point for pain duration as the first encounter with a health-care professional is more objective, but it may also be subject to recall bias if medical records cannot be cross-referenced and will be dependent on the woman's inclination to seek care for her pain, as well as the availability of such services. In the absence of any further clarity, a minimum of 6 months' duration from when a woman considered the pain as impacting on her quality of life might be acceptable. This is consistent with the IASP's 2011 taxonomy,³⁴ which defines chronicity as CPP that has been continuous or recurrent for at least 6 months, but it can also be cyclical over a 6-month period, as in the case of dysmenorrhoea. Even in this definition it is acknowledged that a 6-month time scale is arbitrary; it was chosen because 3 months was considered too short if cyclical pain conditions were to be included.

In the studies selected here, not one defined the location of the pain in any more specific terms than as being in the pelvis or lower abdomen. This may reflect the diffuse nature of the pain found in women who are subsequently found to have PVI, or a lack of detailed reporting within the study reports. The IASP chooses to define pelvic pain as pain perceived to be located in structures related to the pelvis, in either sex, from what is considered the best attempt at localisation by both patient and clinician through history and examination. This still does not define the anatomical boundaries, although locations such as the pelvis, anterior abdominal wall, at or below the umbilicus, lower back and buttocks have been described.⁶⁸

In addition to pain, superficial varices are the symptoms most likely to cause distress to women. We do not yet understand the time frame over which visible varices develop or if there is any relationship between the degree of reflux measured radiologically and the likelihood of the varices becoming externally visible. Whether the strength and integrity of the pelvic floor muscle, analogous to the protective influence of calf muscle pump power,⁶⁹ has any influence on the development of pelvic varices is also unclear. That visible varices are barely mentioned in our selected studies reflects either their rarity among women with PCS or the focus on the radiological definition by the vascular specialists who were predominantly the study authors. Although it is probably unwise to suggest that visible varices are included as an absolute diagnostic criterion, they may be considered within the context of other features in a diagnostic algorithm. It is certainly important to examine the patients, understand the evolution of any varices, explore the problems they cause and document observations for comparison following any treatment.

Pelvic vein dilatation in ultrasonographic or venographic studies is clearly considered a significant determinant for treatment, and yet a consistent definition of the location and extent of abnormal anatomy is lacking. There was no consistency in the description of the observed veins, with pelvic, uterine and ovarian all being used interchangeably. We would suggest that 'pelvic' is the umbrella term to describe veins of the pelvis, but that when venous diameters are described, the correct vein is named. There is no agreed threshold and a greater than twofold variation in those used in the selected studies. OV lumina in asymptomatic women have been reported as having a mean of 4.5 mm [standard deviation (SD) 1.3 mm] for the left vein and 4.4 mm (SD 0.5 mm) for the right vein.⁷⁰ From this study, it is possible to calculate the upper 95% CI as approximately 5 mm, and, thus, OVs above this calibre could be considered abnormal. However, it is uncertain if the absolute OV diameter is predictive of a successful treatment by embolisation, owing to the inconsistency with which the outcome is defined and the anatomy is reported.

Most studies describe a clear and replicable protocol for their imaging studies, but for a clinical diagnostic test to be used with confidence, a minimum standard of reliability and reproducibility needs to be met, particularly in the case of a dynamic structure such as a vein. Limited or poor reproducibility affects the precision of a test.⁷¹ For OV lumen diameter to be considered as a diagnostic test, validation may be achieved by ensuring the reproducibility of the ultrasonic technique and the agreement of interpretation between independent observers, yet only one study reported the use of independent radiologists and this did not report the extent of agreement.⁴⁰ This is important not only in the measurement of OV diameter, but also in the interpretation of reflux in the pelvic veins from Doppler ultrasound.

Unfortunately, even a standardised imaging protocol will not necessarily lead to consistency. The anatomy of the veins of the pelvis can be extremely variable between women; however, they can be described in a general structured manner. The nomenclature recommended by the International Union of Phlebology, the International Federation of Associations of Anatomists and the Federative International Committee on Anatomical Terminology should be employed.⁷² Variations to standard venous anatomy, when observed on the ultrasound examination, should be reported. These include tortuosity of the target vein, duplications, atresia and the presence of anatomic venous variants, although it is acknowledged that these descriptions could be extensive and would, therefore, benefit from being grouped into cogent categories. The diameter of the OV at its most dilated and of the target vein for embolisation (if not the OV) should be stated. The patient's position and whether or not measurements are taken during the Valsalva manoeuvre should be specified.

Women with reflux in an OV or IIV are candidates for embolic treatment. Therefore, documenting the presence of reflux in these veins seen by Doppler ultrasound imaging is important. In the veins of the leg, the presence of venous flow reversal for 0.5–1.0 seconds, on proximal compression or the Valsalva manoeuvre, is widely considered to be indicative of venous reflux in the great saphenous vein. In the pelvis, there is no similar standard, as illustrated by the breadth of descriptions found in this review. Compression of the pelvic veins to elicit reflux is only possible using the Valsalva manoeuvre, and so the ease with which pelvic veins can be evaluated will never be comparable with that for the leg. A single parameter to define PVI is potentially not possible, or ideal. However, a consistent format for describing

the anatomical location of the reflux, the minimum or absolute blood flow rate or refilling time when reflux is observed would be advantageous. About one-quarter of studies went further in describing the extent of the reflux in filling contralateral veins, or vulvar or thigh veins. These observations might be somewhat dependent on the individual's anatomy but could also be indicative of the severity of the incompetence or the position in which the imaging was performed.

Although a combination of a directed physical examination and Doppler ultrasound imaging is usually sufficient to characterise the anatomic and functional extent of PVI, diagnosis is usually confirmed by venography immediately prior to embolisation, and these results and their consistency with ultrasound should be reported. The extent to which this occurs in the literature will be discussed in *Chapter 5*. When initial assessment is performed using CT or MRI, instead of ultrasound, the reason for their use should be specified, the results should be reported in the same manner as for ultrasound, and the specific criteria used for diagnosis of PVI should be indicated.

Conclusion

A handful of studies attempted to use or create a scoring system, while two authors have proposed division of PVI into four categories, the most common of these being OV reflux.^{49,53} An algorithm to diagnose and subcategorise PCS, or even to rank the severity of the condition, would be clinically useful and would help resolve inconsistencies between study reports. Such work has been undertaken in other pain-related conditions⁷³ to determine the best combination of variables for the derivation of data-driven algorithms with optimum sensitivity and specificity relative to the reference diagnosis. With PCS, there is no independent gold standard for a diagnosis other than venography, as all current definitions include both clinical and radiological observations. A consensus diagnosis involving venography cannot be derived without incorporation bias (the inclusion of the test of interest in the reference diagnosis).

The synthesis of current literature is hampered by the absence of clear, consistent diagnostic criteria. Thus, the first aim should be to achieve consistency on the descriptions of symptoms and, from there, document comprehensive cohorts of women presenting with CPP using these definitions, and also those pathological conditions that would rule out a diagnosis of PCS. A consensus definition would improve the current situation and improve multidisciplinary working between gynaecology, where women typically present, and interventional radiology.

We propose a potential scoring template that may be adopted for reporting standards for clinical research studies evaluating the diagnostic tests for PCS and the effectiveness of treatments for PVI (*Table 2*). This would facilitate consistency to allow future comparison between the results of different studies, and would improve the overall quality of clinical research in this field to the standards found elsewhere in research on venous disease.⁷⁴ The proposed thresholds for considering PCS unlikely, moderately likely or highly likely are not statistically derived and represent the opinion of the authors, but they also reflect the prevailing consensus of relative importance of symptoms and observations seen in this review.

Further work is essential to refine and validate the proposed scoring system. Ideally, the diagnostic performance of each individual criterion would be evaluated for its ability to discriminate PCS from pain-free controls, and those parameters with a statistically significant difference would be incorporated into a logistic regression model. The regression coefficients of the best-fit model could be used to weight scores for each criterion. The individual and total scores would then be mapped onto a receiver operating curve to determine the cut-off value that provides the optimum clinical performance with respect to sensitivity and specificity. Finally, the scoring system would be validated in a prospective study of women with CPP to determine its accuracy. This strategy would have to accept the issue of incorporation bias and also be contingent on the use of modern ultrasound methods. This would then provide a practical, valid tool for clinical use that would assist in the identification of women for invasive confirmatory venography and, potentially, treatment. In the meantime, the proposed template may be considered useful.

TABLE 2 Suggested diagnostic and scoring criteria for PCS

Criterion	Diagnostic standard	Proposed score	Obtained by
CPP, considered by the woman to impact on her quality of life, of a duration of > 6 months, located in the pelvic region below the umbilicus	Presence of CPP	Score: 0 for < 3 months, 1 for 3–6 months and 3 for \geq 6 months	Taking a history from women
Delineation of pain symptoms and severity	Presence of each of dysmenorrhoea, dyspareunia and pain after prolonged periods of standing	Dysmenorrhoea score: 0 for absent or 1 for present Dyspareunia score: 0 for absence or 1 for presence Pain after prolonged periods of standing score: 0 for absence or 2 for presence	VAS of 0–100 mm for each pain symptom, with recall period of 3 months and options to define as not applicable
Visible varices	Presence and location of visible varices	Lower-leg score: 0 for absence or 1 for presence Upper thigh, buttocks or vulva score: 0 for absence or 2 for presence	Clinical examination
Pelvic vein anatomy	Presence of pelvic vein variants	Score 0 for absence or 2 for presence	Assessment of high-resolution TVUS images
OV dilatation	Diameter of OV at widest calibre	Score 0 for diameter < 4 mm, score 1 for diameter 4–5 mm and score 3 for diameter > 5 mm	Assessment of high-resolution TVUS images or MRI
Reflux in pelvic veins	Presence of retrograde flow on Valsalva manoeuvre Refilling time Observation of filling of contralateral veins	Score 0 for absence or 2 for presence of retrograde flow Score 0 for < 20 seconds or 1 for \geq 20 seconds Score 0 for absence or 2 for presence of contralateral filling	Assessment of power Doppler TVUS images
Score out of maximum 20		PCS unlikely: < 10 PCS moderately likely: 10–14 PCS highly likely: \geq 15	

VAS, visual analogue scale.

Chapter 4 A review of the association between pelvic vein incompetence and chronic pelvic pain

Introduction

There are many studies reporting a relationship between radiological observations of incompetent (dilated and refluxing) pelvic veins and CPP, but these do not, on their own, establish causation between PVI and CPP. To do this, the criteria for causality proposed by Hill⁷⁵ should be examined sequentially, using statistical principles, and convincing evidence should be sought for each. We first consider the types of study and the data required as evidence.

Strength of association

The stronger the association between risk factor (incompetent pelvic veins) and outcome (CPP), the more likely it is to be causal. A case-control study of women with and without CPP who have undergone a valid method of pelvic vein imaging, with dilatation and reflux defined by acceptable criteria, would provide data on the odds of CPP being associated with and without PVI. A highly significant odds ratio would provide strong evidence of association.

Consistency of findings

If an association is replicable in different populations, whether defined by ethnicity, parity or country of study, this provides reassurance that any observed association is not confounded by the study population.

Specificity of the association

If incompetent veins were frequently observed alongside another known or presumed cause of pelvic pain symptoms, for example endometriosis, it would be difficult to establish whether or not each risk factor independently caused CPP, whether or not there was synergy or if one was a confounding factor of the other. Studies of women with CPP subdivided into groups according to whether or not pathology was observed at laparoscopy would assist with this distinction.

Temporal sequence of the association

To suggest a causal link, the emergence of incompetent veins should occur before the onset of pelvic pain. Strong evidence for temporality would require the screening of asymptomatic women for pelvic vein anomalies and following their life course to identify those who develop CPP, whereas pelvic venography is usually instigated as a result of CPP.

Biological gradient

An observation of greater pain with a higher degree of dilatation or severity of reflux, or number of vessels involved, may imply causation. Yet pain is a highly subjective outcome and, if viewed from a biopsychosocial perspective, organic pathology, anxiety trait and coping skills after being given the diagnosis could all be expected to contribute to a woman's experience of pain, which may then modify any relationship between anatomy and symptom severity.

Biological plausibility

A potential physiological mechanism that links pelvic vein dilatation or reflux to the experience of pelvic pain would add weight to the evidence for causation. Pelvic varices are seen as an engorgement of blood, pooling in the pelvic veins, which is consistent with the sensation of a heavy and dragging pain described by women diagnosed with PCS. The pain often improves when a supine position is adopted, as the venous dilatation resolves with draining of the venous system.

Coherence

The analogy with saphenous varicose veins, which can cause feelings of heaviness, aches and discomfort in the leg, supports the hypothesis that incompetent pelvic veins can cause CPP.

Experiment

A convincing piece of evidence would be if the removal or improvement of reflux or dilatation in the pelvic veins resulted in a sustained decrease in the perceived CPP. Interventional radiology techniques such as embolisation can selectively block pelvic veins. There are considerable data on the reduction of pain following embolisation, but the quality of the evidence is doubtful. The efficacy of these techniques will be considered in *Chapter 6*.

Objectives

This chapter describes a review of studies that assess the relationship between PVI and CPP in women, and to consider the strength of evidence for causation. Secondary objectives were to review studies that looked at the relationship between PVI and venous insufficiency in the lower limbs, and to estimate the prevalence of PVI in an unselected population.

Methods

We planned a review of any study in which the relationship between PVI and CPP could be explored. This could include case–control studies involving groups with and without CPP who undergo pelvic vein imaging or, conversely, groups of unselected women undergoing pelvic imaging in which a history of CPP is sought. At the outset, it was considered unlikely that any prospective cohort studies would exist that captured both pain and pelvic imaging data.

Given the two angles that potential studies could take, from pain or screening populations, and the breadth of search terms that would be required to encapsulate these concepts, a review specific search strategy was not developed. Instead, the studies considered after the initial screen for the systematic reviews of accuracy and effectiveness, described in *Chapters 5* and *6*, were also screened for potentially relevant studies.

At the outset, it was not anticipated that any meta-analysis would be possible. The quality of studies identified was assessed using the Newcastle–Ottawa Scale for observational studies.⁷⁶

Results

There were six association studies that we considered eligible for inclusion in this review.^{6,16,23,40,77,78} A further four studies considered the prevalence of PVI in non-pain populations^{68,76,79,80} and three studies investigated the relationship between PVI and venous insufficiency of the lower limbs.^{37,77,81}

The quality assessment of the case–control studies is summarised in *Table 3*. Generally, the quality was acceptable, although cases and controls were usually of similar numbers and not determined by an a priori sample size.

TABLE 3 Newcastle–Ottawa Scale of quality of case–control studies of pelvic pain and PVI

Study (author and year)	Case definition	Representativeness	Selection of controls	Definition of controls	Comparability	Exposure ascertainment	Same method for both	Non-response rate
Beard <i>et al.</i> 1984 ¹⁶	Yes: independent validation	Yes: series of cases representative	Hospital controls	No history of disease (no gynaecological symptoms)	No	Unclear	Unclear	Yes
Beard <i>et al.</i> 1988 ⁶	Yes: independent validation	Yes: consecutive	Hospital controls	No history of disease in either control group (no evidence of PCS on venography, or in group admitted for sterilisation)	Yes	Structured questionnaire and clinical examination	Yes	Yes
Halligan <i>et al.</i> 2000 ²³	Yes: independent validation	Yes: consecutive	Hospital controls	No history of disease (CPP and PCS)	Yes	Questionnaire, history and clinical examination	No	Yes
Park <i>et al.</i> 2004 ⁴⁰	Yes: independent validation	Yes: series of cases representative	Hospital controls	No history of disease (healthy controls with no pelvic pain or pelvic abnormality on TVUS performed for routine gynaecologic examination)	Yes	Clinical features and selective ovarian venography	No	Yes
Bora <i>et al.</i> 2012 ⁷⁷	Yes: independent validation	Yes: all referred for abdominal–pelvic imaging	Hospital controls	No history of disease (PCS or dilatation of pelvic veins)	Yes	Clinical features and results of pelvic imaging	Yes	Yes
Motta-Ramirez <i>et al.</i> 2013 ⁷⁸	Yes: independent validation	Yes: all women with the required symptoms were included	Unclear	Unclear	Unclear	Imaging studies	Unclear	Yes

Association of pelvic pain and pelvic vein incompetence

All reviews of the association between PVI and CPP, and the diagnosis PCS, refer back to the seminal paper of Beard *et al.*¹⁶ His team performed transfundal venography on 81 women, although 18 were excluded owing to a failure to produce adequate images. The women were classified into three groups: 45 women with CPP and no apparent pathology at laparoscopy (the presumed PCS group), 10 with CPP and endometriosis, adhesions or pelvic inflammatory disease, and eight with no pain and no pathology observed during laparoscopic sterilisation as controls. Owing to the nature by which the controls were chosen, they were older on average and all were parous. Venographic parameters reported were the maximal OV diameter, contrast clearance time and congestion, which combined variation in the OV diameter and the extent to which the veins were tortuous. A ranking of 1 to 3 was assigned to different grades of severity within each variable, allowing a score to be derived.

A statistically higher OV diameter was observed in the idiopathic CPP group than in the other two groups [mean difference idiopathic CPP vs. control 3.48 mm ($p < 0.005$); mean difference idiopathic CPP vs. pain and pathology group 3.13 mm ($p < 0.004$)], and also slower clearance, with contrast still visible after 40 seconds in 26 out of 45 women (58%). Minimal tortuosity was seen in two of the eight control-group women and one woman with pathology, compared with 38 (84%) women with idiopathic CPP exhibiting moderate or extensive congestion. A venogram score of ≥ 5 gave a sensitivity of 91% (95% CI 79% to 98%) and specificity of 75% (95% CI 35% to 97%) for idiopathic CPP compared with the controls and the same sensitivity and a specificity of 100% compared with those with CPP and pathology.

This team followed up their work with another study of 68 consecutive women with a history of CPP and 36 pain-free controls undergoing sterilisation.⁶ All underwent laparoscopy and most had a venogram, with 25 having identifiable pathology, of whom 22 had normal venograms. Of the 43 women with no pathology, 35 had evidence of PVI, giving a prevalence of 52% among women in pelvic pain clinics, and statistically significant negative association between pathology and PVI, although three women did exhibit both. The team went on to evaluate the relationship between particular symptoms and PVI, with post-coital ache [23/35 with evidence of PVI vs. 3/36 in control group ($p < 0.0001$) and vs. 2/22 with pathology and no PVI ($p < 0.001$)] and ovarian point tenderness [22/35 with evidence of PVI vs. 5/36 in control group ($p < 0.0001$) and vs. 4/22 with pathology and no PVI ($p = 0.01$)] exhibiting the highest discriminatory ability between those with PVI, those with pathology and those without either. The authors attribute compression of the OV and back pressure to this observation and also noted that this sign occurred on the side that the women reported was painful.

Conflicting evidence of the association of PVI and CPP came from a study of women recruited from a pelvic pain clinic, with suspicion of PVI, who underwent transvaginal Doppler ultrasound and transfundal venography.²³ Venographic evidence of PVI, defined as a score of ≥ 6 out of 9 on the PVI scoring system,¹⁶ was confirmed in 36 women. Ultrasound assessment of PVI in these women was compared with that of 19 asymptomatic women, the majority of whom underwent the ultrasound to confirm placement of an intrauterine contraceptive device but had no other organic pathology likely to cause pelvic pain. The modified PVI scores from ultrasound were unable to discriminate the venography-confirmed PVI cases from the controls (mean modified PVI ultrasound score 5.1 in PVI cases vs. 4.5 in controls; $p = 0.182$). The authors considered whether or not this was due to the Doppler ultrasound being insensitive to low flow rates or distorted by tortuosity, or by its use on patients in the supine position. The PVI cohort may have been defined by a threshold on the scoring system that was too low, or that contained women who had other causes of pain or were otherwise different as a result of their lower age. Furthermore, there were statistically significant differences in the uterine volume (mean difference 26.9 cm³; $p = 0.008$) and endometrial thickness (mean difference 4.5 mm; $p < 0.001$), with a small volume seen in women with PCS and a thinner endometrium, although this may be attributable to the high rate of intrauterine contraceptive device use in the control group. As with other studies,¹² polycystic ovaries are more frequently observed in women with PCS (total follicular area 0.4 cm² larger in PCS group; $p = 0.01$).

In a Korean study, 32 women with clinical evidence of PCS, no other pathology and CPP, first had pelvic varices identified by ultrasound, with PVI confirmed by selective OV venography using > 5 mm OV diameter and various reflux features as criteria.⁴⁰ The control group, who were of a similar age, were asymptomatic and had no other pathology. The positive predictive value was maximal at 83% with a 6 mm OV diameter threshold on transabdominal TAUS, and a statistically significant increase in mean left OV diameter in those with CPP compared with controls [7.9 mm (SD 2.3 mm) vs. 4.9 mm (SD 1.5 mm) respectively; $p < 0.001$] was observed using this technique. By transvaginal Doppler ultrasound, 100% of the CPP group and 17% of controls had pelvic varices. There was a statistically significant difference in the mean bilateral OV diameters (e.g. a difference of 2.6 mm in the left OV; $p < 0.0001$) but not in the uterine volume. Polycystic changes in the ovary were also more frequent in the PCS group (41% vs. 11%; chi-squared test $p < 0.006$).

Seventeen women, out of 1800 who had had pelvic CT scans and no other abdominal or pelvic pathology, were described as having PVI.⁷⁸ Twelve of these women were reported to have CPP.

A large series of 725 women undergoing TAUS and 402 having a pelvic CT were assessed for venous insufficiency in the lower limbs and also questioned regarding CPP.⁷⁷ Using a threshold diameter in the OV of 5 mm, 21 women had dilated veins by ultrasound and 35 had dilated veins by CT. They found a significant relationship with CPP, with 51 of 56 (91%) of those with dilated pelvic veins reporting pain, compared with 8% of the non-dilated group (chi-squared test $p < 0.0001$).

A summary of these five studies is provided in *Table 4*. Owing to the considerable heterogeneity, the odds ratios were not pooled in a meta-analysis.

A further insight into pelvic anatomy came from a case-control study involving 25 women with a history of CPP with no obvious cause and an equal number of comparable, pain-free women undergoing a routine gynaecological check-up.⁷⁹ All women had transvaginal Doppler ultrasound that measured the resistance and pulsatility indices of the uterine artery instead of assessing venous flow. The authors found that indices were significantly lower in women with CPP than in asymptomatic controls, in contradiction to results from women with primary dysmenorrhoea,⁸¹ where these indices were lower in the pain-free controls. Again, there was no difference in uterine volume but the ovaries were not assessed. Without assessment of the corresponding venous system, the significance of these findings is unclear.

Prevalence of pelvic vein incompetence in asymptomatic populations

Populations of women undergoing detailed pelvic imaging for other reasons provide data on the incidence of PVI in asymptomatic populations. A retrospective study of the preoperative helical CT scans of female kidney donors provides data on the incidence of OV varices and incompetence in an asymptomatic population.⁸² An OV diameter of > 7 mm was considered to be dilated, whilst reflux was complete opacification during the arterial phase of CT angiography; this latter observation defined incompetence. Medical note review implied that no women reported pelvic or abdominal pain, although 4 out of 34 had small fibroids. The prevalence of PVI was 47% (16 of 34 women), all in the left side, six with bilateral incompetence. The mean diameters were 9.1 mm for the left OV and 8.8 mm for the right OV. A statistically significant association of PVI with parity was observed, with 15 out of 16 with PVI compared with nine of 18 without being parous (chi-squared test $p = 0.005$).

A study of the preoperative angiography results of female kidney donors also provides data on PVI prevalence.⁸³ The authors used the venous phase of the angiogram to evaluate the OV, with a threshold of 8 mm to define a varice. Women with this diagnosis were asked to complete a questionnaire about CPP before and 6 months after they underwent left nephrectomy. Of 273 women whose aortograms were reviewed, 27 (9.9%) were found to have PVI in the left OV. Within this group, 22 completed the questionnaire and 13 (59%) reported pelvic pain before the surgery. The authors also remarked that nephrectomy requires OV ligation, used as a treatment for PCS, and noted that seven gained complete relief (54%) and three gained partial relief (23%) of pelvic pain.

TABLE 4 Summary of studies exploring PVI and its relationship with pelvic pain

Study (author and date)	OV dilatation/PVI confirmed by	CPP/case definition	OV dilatation and/or PVI rate (PVI present/total in study)	% of those with PVI having CPP	% of those with CPP having PVI
Beard <i>et al.</i> 1984 ¹⁶	≥ 5 of 9 on transfundal venogram score	History of > 6 months and negative laparoscopy	43/61 (68%)	41/43(95%)	41/45 (91%)
Beard <i>et al.</i> 1988 ⁶	≥ 5 of 9 on venogram score	Idiopathic CPP (vs. pathological)	38/68 (55%)	35/38 (92%)	OR 31 (95% CI 5 to 205; <i>p</i> < 0.0004) 35/43 (81%)
Halligan <i>et al.</i> 2000 ²³	≥ 5 of 9 on ultrasound score	Women in CPP clinic in whom venography established PVI	29/55 (52%)	21/29 (72%)	OR 32 (95% CI 8 to 134; <i>p</i> < 0.0001) 21/35 (60%)
Park <i>et al.</i> 2004 ⁴¹	TAUS and TVUS. OV threshold > 5 mm, venous flow reserved or static	CPP of > 6 months and ovarian point tenderness	37/60 (62%) PVI	32/38 (84%)	OR 2 (95% CI 0.7 to 6; <i>p</i> = 0.211) 17/26 (65%)
Bora <i>et al.</i> 2012 ⁷⁷	> 5 mm OV by TAUS	Not defined, women undergoing lower-limb assessment	OV dilatation: 17/37 (46%) Pelvic varices: 38/67 (57%) 55/1029 (5%)	51/56 (91%)	OR 1.3 (95% CI 0.5 to 4; <i>p</i> = 0.6) 32/32 (100%) 51/129 (39%)
Motta-Ramirez <i>et al.</i> 2013 ⁷⁸	CT scan showing arterial phase opacification and retrograde venous flow	Described as abdominopelvic pain syndrome, excluded other abdominal conditions	17/1800 (0.9%)	12/17 (71%)	OR 117 (95% CI 45 to 301; <i>p</i> < 0.0001) Data incomplete

OR, odds ratio.

Another retrospective review of pelvic MR angiograms of 22 female kidney donors found that eight had indirect evidence of reflux in the left OV, with a mean diameter of 6.4 mm (SD 0.8 mm), 13 had no reflux and 1 OV could not be located, giving a prevalence of 38%.⁷⁰ From this cohort, 19 had an adequate clinical history, confirming the absence of CPP in all.

In a large series of 324 women who had undergone multiplanar CT for reasons other than CPP, right OV variants that drained directly into the right renal vein were identified in 32 (9.9%).⁸⁴ Of these women, three exhibited left OV reflux and one exhibited right OV reflux with predominant right pelvic varices, defined as veins of > 5 mm. Dilated pelvic veins were identified in 59 of the 324 women, and reflux in 57 of these 59 women, of which all but one were predominantly in the left OV. There was no statistical difference for the presence of pelvic varices between women with and women without a right OV drainage variant ($p = 0.3$). There was no significant difference in the diameter in either OV between women with and women without a right OV variant, but there was a significant difference between the parous and nulliparous women. OV reflux was identified in 17.6% of this population. These authors noted that two women did not have left OV reflux but still had pelvic varices, but they conclude that this may be due to the limitations of CT imaging, which is performed while the patient is in the supine position. This study may provide indirect evidence that drainage from the OV directly into the renal vein might not be a primary factor in the development of pelvic varices, as junctional variations of the right OV did not seem to be associated with reflux and pelvic varices.

Relationship with varicose veins of the lower limbs

Pelvic varices are often incidentally observed during investigation of varicose veins of the lower limbs, using colour Doppler ultrasound, the standard method for assessing superficial venous insufficiency. In a large cohort of women undergoing lower-limb assessment and classified using the Clinical, Aetiological, Anatomical and Pathophysiological (CEAP) criteria⁸⁵ as being between zero and five, without a history of deep-vein thrombosis, 249 had TVUS with Doppler and 59 had selective venography.³⁷ The prevalence of reflux of pelvic origin into the lower limbs was 124 out of 1020 (12.2%), roughly equally distributed between bilateral and unilateral. In a subsample of this cohort, 150 out of 249 (60.2%) women had pelvic varices seen by TVUS with Doppler, with a mean diameter of these veins of 8.5 mm (SD 1.7 mm). The positive predictive value of reflux of pelvic origin in the lower limb for observation of a pelvic varice was 49%, and negative predictive value was 94%. Assessment of the lower limbs, therefore, cannot be the sole test for PVI, and so the authors suggest that pelvic pain be considered before further TVUS investigation. However, whenever a negative result from colour Doppler ultrasound of the lower limbs is observed, further investigation of pelvic veins is not necessary. A statistical significant relationship between lower-limb reflux of pelvic origin and recurrent varicose veins was observed, suggesting an important and unrecognised cause of recurrence.³⁷

A similar study of 100 women, all reporting CPP of unknown origin, investigated the relationship pelvic varices and previously undiagnosed lower-limb venous insufficiency.⁸¹ Using a threshold of 5 mm OV diameter, the prevalence of varices was 30%, with a positive predictive value of lower-limb insufficiency for pelvic varices of 77% and negative predictive power of 87%. An additional observation was that there was no difference in the incidence of ovarian cysts between those with and those without OV varices.

The series of 1029 women described above were also assessed for venous insufficiency in the lower limbs.⁷⁷ Using a threshold diameter in the OV of 5 mm, 56 women had dilated veins and lower-limb venous insufficiency was found in 44 of these.

Discussion

Summary of key findings

Overall, there is a lack of well-designed case–control studies to delineate the relationship between CPP, dilated pelvic veins and PVI. In the five case–control studies with appropriate data amongst those assessing the association between pelvic pain and PVI, the associations were generally fairly similar,^{6,16,23,40,77} with three studies showing statistically significant associations (odds ratios of between 31 and 117).^{6,16,77} The two smallest studies failed to reach statistical significance in the odds of association, perhaps because they were too small for a difference to be detected. The proportion of women found to have PVI who reported CPP ranged considerably, from 39% to 91%. Polycystic ovaries were observed more frequently in the group with CPP and PVI in two studies. The prevalence of PVI ranged considerably, although the majority of women with PVI had CPP. Conversely, in the four studies of asymptomatic women, no more than half had PVI, although again the prevalence ranged widely. Where lower-limb venous insufficiency was seen, between 60% and 77% of women also had pelvic varices.

Strengths and limitations of review

We could be criticised for not conducting a search specific to this review question, potentially missing important citations. In screening several thousand citations for the reviews of imaging methods and the effectiveness of embolisation, we located all of the papers included here. Moreover, in the process of reviewing the shortlisted studies for these other reviews, we scanned the reference list for additional relevant papers and did not locate any additional contemporary papers. Some papers refer to classical studies such as those by Taylor and Hobbs,^{8,11} but these predate the advent of diagnostic laparoscopy or deployed insensitive imaging techniques. We are therefore confident that we have located all relevant case–control studies, although we may have missed some studies which focused primarily on lower-limb insufficiency, with the coexistence of PVI a secondary consideration.

The six most pertinent studies were unfortunately of mixed methodological quality, drew on clinically disparate populations and defined PVI inconsistently, making it inappropriate to pool the results. The first study of Beard *et al.*¹⁶ used a control group who were older and of higher parity, which may have confounded the groups, while other studies retrospectively identified the pain status of the participants after venography, with considerable potential for the underidentification of pain. The selection of controls for this type of study can undermine the conclusions drawn if they are either too disparate or overmatched. Ideally, there should be considerably more controls than cases to improve the power of the analysis, whereas the reverse was true in the studies by Beard *et al.*¹⁶

Interpretation

In reviewing the data for evidence of a causal association between PVI and CPP, we should refer back to the criteria of strength, consistency, specificity and a biological gradient, which can be addressed by the studies located in our review.

The studies of the association between PVI and CPP are varied, making us reticent to conduct meta-analysis and denying us the opportunity to derive a pooled estimate of the odds of association between PVI and CPP. The study by Park *et al.*⁴⁰ perhaps represents the most robust data, with standardised contemporary imaging techniques and comparable controls in terms of age, but defines presence of reflux from ultrasound rather than venography, potentially miscategorising some of those whose blood flow appeared normal. The difference in left OV diameter was statistically significant between the groups, but unfortunately the data could not be disaggregated to construct a receiver operating curve to determine an optimal threshold, and, overall, the study had only 7% power to detect a statistically significant association given the odds ratio observed. Other studies produced highly significant odds ratios that would suggest a strong association between PVI and CPP that is possibly consistent across study settings. The ambiguity and inconsistency with which PVI is defined, as discussed in *Chapter 3*, may explain the differences between studies, as might the imaging method, with supine ultrasound potentially under-recognising reflux. As no study conducted an a priori sample size calculation, it is also possible that a significant relationship has been missed in some of the smaller studies.

The studies of Beard *et al.*^{6,16} provide some reassurance that PVI is not frequently observed alongside other pathology such as endometriosis, and, therefore, the pain could possibly be attributed to the observed PVI. In their first study, the odds of association were higher when comparing the cases against the group of women with CPP and pathology than against the non-pain control group, although numbers were very small. This was replicated in their second study, which compared an idiopathic CPP group against a group who mainly had confirmed endometriosis.

There are no prospective cohorts to address the issue of temporality or studies that attempted to rank PVI severity and pain intensity. All cases were defined by a clinical history of CPP and, unlike some of the studies of embolisation, did not ask women to complete visual analogue scales to score their pain. Pain is highly subjective and individual, and so might never exhibit a proportional relationship with any ranking of PVI severity. An analogous situation occurs in endometriosis, whereby the relationship between the degree of endometriosis and the amount of pain experienced by the woman does not always seem correlated.⁸⁶

The study of potential kidney donors is a fortuitous method of establishing the prevalence of PVI in general populations, and in the left OV in particular, as laparoscopic donor nephrectomy tends to be performed on the left kidney. Prevalence of PVI in the left OV was variously reported at 10%, 17%, 18%, 38% and 47%.^{70,82-84,87} The varying thresholds for defining OV dilatation may give rise to these differences, as might the imaging systems deployed, although no apparent association can be deduced here. CT may overmagnify vessel diameters by 20% yet be unable to detect small veins, and some distention of the OV may occur as a result of the increased intra-abdominal pressure caused by breath holding. Two studies both used CT and a threshold of 5 mm to define dilatation in the pelvic veins and yet prevalence of varices were 9% and 18%, respectively.^{77,84} Belenky *et al.*⁸³ argued that detected retrograde venous flow by renal artery angiography is preferable as it is physiological, whereas selective venous catheterisation may aggravate reflux. Nascimento *et al.*⁷⁰ remarked that the MR angiography technique they used was suboptimal and led to less indeterminate determination of blood flow, in addition to the general issue of undertaking the scans in the supine position and with breath holding.

The variation may also be explained by factors such as parity, age and ethnic group, but it illustrates that PVI is ubiquitous and relatively common. Ahlberg *et al.*⁸⁸ examined the venous structure in cadavers and reported the complete absence of valves in 15% of left OV and 6% of right OV, with half of women exhibiting incompetent valves.

Belenky *et al.*⁸³ provide good data on the incidence of OV varices in an unselected population, but they do not support the hypothesis that OV varices are invariably symptomatic, with 41% of patients not reporting CPP prior to their nephrectomy, suggesting that other mechanisms contribute to PCS. With retrospective recall of preoperative pain, this finding may be subject to recall bias and also precluded further examination by a gynaecologist to explore other sources of CPP. Furthermore, 4 of the 22 responders were peri- or postmenopausal, with others claiming that PCS is a condition experienced solely by women of reproductive age.⁶ Finally, the study has the same limitation as that noted with CT imaging, in which the supine position and inability to perform the Valsalva manoeuvre underestimates the incidence of reflux.

There appears to be a significant relationship between the presence of pelvic varices and lower-limb venous insufficiency, suggesting that where pelvic varices are identified, the superficial veins should also be assessed with colour Doppler ultrasound, as the underdiagnosis of leg varicosities is likely. Early identification would prompt treatment, reducing the likelihood of consequent ulceration and unsightly leg veins. Evaluation of the pelvic venous system when lower-limb venous insufficiency is found does not yield very many additional observations of pelvic varices in the absence of pain.

Conclusion

There is insufficient evidence to categorically state that PVI is the cause of CPP in women with no other pathology. There are strong associations in some studies, although there is significant heterogeneity among the reviewed studies, which also have some methodological weaknesses related to the control groups. A large, well-designed case-control study, using contemporary imaging techniques and clear criteria for the ascertainment of both CPP and PVI, is required to help to remove the residual doubt about the relationship between the two phenomena.

Chapter 5 A systematic review of the accuracy of non-invasive imaging techniques in the determination of pelvic vein incompetence

Introduction

The accuracy of tests used to diagnose PCS is influenced by the variation in definitions for this syndrome, as discussed in *Chapter 3*. Most studies of PCS exclude women with demonstrable endometriosis or adhesions, among other conditions, as these are considered to be the more likely causes of pain. Although laparoscopy plays an important role in the differential diagnosis of CPP, it cannot categorically identify PVI. The diagnostic venogram gives immediate dynamic flow information and measurements of pelvic veins and is considered the gold standard for the identification of PVI. Venography has the option of tilting the patient position and the patient can be asked to perform the Valsalva manoeuvre to further delineate venous reflux.

However, venography involves the use of contrast and is invasive, and so other methods of screening for PVI are usually employed, including ultrasound with some form of Doppler assessment of blood flow parameters, CT and MR venography. As conventional venography is usually undertaken immediately prior to treatment with embolisation, it is important that any screening test used to triage patients is capable of detecting all of those patients in whom PVI would be detected by venography, with such a combined strategy having greater specificity than venography alone.

Objectives

This chapter describes a systematic review of the diagnostic test accuracy of non-invasive imaging tests for the diagnosis of PVI in women with CPP, when compared with the gold standard of fluoroscopic selective venography.

Methods

The systematic review was conducted based on a protocol developed prior to commencing the review and registered with the PROSPERO database. The protocol was designed using widely recommended methods for conducting reviews of interventions and is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Standards for Reporting of Diagnostic Accuracy standards.

Search strategy

A thorough and comprehensive literature search was developed. This was used in the following widely recognised databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library, Database of Abstracts of Reviews of Effects (DARE), EMBASE (Excerpta Medica Database), Latin American and Caribbean Health Sciences Information System (LILACS), MEDLINE (Medical Literature Analysis and Retrieval System Online), Medion, Scientific Electronic Library Online (SciELO) and Web of Science. International databases including African Index Medicus (AIM), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR), Pan American Health Organisation (PAHO), Population Information Online (Popline) and Western Pacific Region Index Medicus (WPRIM) hosted by the World Health Organization were also searched. Searches were from database inception to March 2014.

Our search term combinations consisted of medical subject heading subheadings, text words and word variations. For our population, the terms 'pelvic congestion syndrome', 'chronic pelvic pain', 'dyspareunia' and 'dysmenorrhoea' were then combined with terms for imaging tests including 'ultrasound', 'magnetic resonance imaging', 'computer tomography', 'angiography', 'phlebography' and 'venography'. Wildcard characters were used to capture alternative spellings and stems of words. This search strategy was modified to suit to each database being searched. The search was restricted to 'humans' and 'females'. Bibliographies of all relevant primary articles and reviews were also hand-searched to identify any articles missed by the electronic searches. A comprehensive database was constructed using Reference Manager 12.0 (Thomson ResearchSoft, San Francisco, CA, USA) to store all identified references. No language restrictions were applied in the searching process.

Study selection and data extraction

Studies eligible for inclusion in the review were selected in a two-step process. First, citations identified by the electronic database searches were screened, predominantly by a single reviewer, based on their titles and abstracts, for relevance to pelvic pain. Full manuscripts were obtained for those citations that met or potentially met the predetermined inclusion criteria. Two reviewers then independently inspected the manuscripts to confirm that they fulfilled the following criteria:

1. Population – women with a clinical diagnosis of CPP. No restriction was placed on any previous treatment, age of the participants, duration of symptoms, comorbidity (including the copresence of endometriosis or other gynaecological cause) or severity of the complaint in selection of the studies.
2. Index test – any non-invasive imaging test, including TAUS or TVUS with or without Doppler (duplex, colour, power), MRI, MR venography, CT and CT venography. Phlebography was accepted as an equivalent term, while descriptions of angiography were reviewed to see if a venogram was actually performed. Where conventional CT or MR scans were undertaken before CT or MR venography, respectively the latter was considered to be the index test.
3. Reference test – confirmatory diagnosis by fluoroscopic venography. Venography could be transfundal (injection into the myometrium of the uterus) or transcatheter (via the femoral, jugular or another vein). Phlebography was accepted as an equivalent term, while descriptions of angiography were reviewed to see if a venogram was actually performed.
4. Outcome – diagnosis of PVI, by whatever method or criteria.
5. Study design – studies in which index test and reference standard were performed in the same individuals. We anticipated that studies may not have been designed as classical test accuracy studies, and may use the index test as a method of screening prior to venography and potentially embolisation. These were included in reviews where data were reported on the index test findings.

Studies were excluded if the reference standard was not performed alongside (or within 1 year of) the index test. Similarly, studies were also excluded if only the reference standard was undertaken or where there was insufficient description of the findings of the index test to allow attempts at data extraction for a 2 × 2 table. Retrospective studies, where the population was those undergoing embolisation and where it could not be determined how many patients had initially had the index test, were also excluded.

Two reviewers independently assessed the full-text papers to determine if they met the above criteria. Any disagreements surrounding the eligibility of a paper were solved through consensus. Data were extracted on study characteristics and methods, with any limitations described by the authors noted. Data were collated on study characteristics, including methods of recruitment, patient characteristics, outcomes and results. If a study undertook more than one imaging test, the data were extracted separately. Results from the studies were used to generate 2 × 2 tables where possible, cross-classifying index test results and venographic diagnoses.

Methodological quality assessment

The methodological quality of all the papers fulfilling the inclusion criteria was assessed by both reviewers and consensus achieved. Quality was defined as the confidence that the study design, conduct and analysis minimised bias in the estimation of test accuracy. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Study (QUADAS) tool.⁸⁹ The original publication of this checklist identified 14 items for assessment; 11 of these are included in the Cochrane version of the tool and it is this version that was used for this review. The three excluded QUADAS items relate to the quality of reporting rather than to methodology. We further chose to not include the question regarding whether or not the same clinical data would be available when test results were being interpreted, as would be available when the test is used in practice, as we felt that the nature of the tests being evaluated and the clinical context made this redundant. Therefore, our quality tool consisted of 10 quality questions, which are described in *Table 5*.

Data synthesis

Data on the number of women with CPP found to have or not have PVI on non-invasive imaging were used to populate 2 × 2 tables, extracted from the study reports in duplicate. Where possible, the sensitivity and specificity were calculated. The objective was to obtain pooled estimates of sensitivity and specificity where it was possible and appropriate to do so. We anticipated three types of outcome: a continuous measure of OV diameter, potentially with different studies using different threshold in their definition of excessive dilatation; a dichotomous description of either dilatation, tortuosity or reflux; or an ordinal outcome of the degree of reflux, such as slow, reversed or absent blood velocity.

A meta-analysis was considered if there were more two or more studies using the same non-invasive test and providing sufficient data to extract data into a 2 × 2 table for any one outcome. Depending on the type of outcome, the summary statistics that would be estimated would be either the pooled sensitivity and specificity for dichotomous outcomes or the expected receiver operating curve (ROC) curve for a test across many thresholds (the summary ROC curve) for continuous variables, using Review Manager 5.1 (2011, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Ultimately, meta-analysis was not considered possible.

TABLE 5 Quality checklist for studies of non-invasive tests for determining PVI

Criteria	Decision
Was the spectrum of patients representative of the patients who will receive the test in practice?	Y, N, U Y if the study population was women with CPP, N if it selected the population on the basis of either index or reference test, or if it included women having the index test for other reasons, e.g. venous insufficiency of the lower limb, U if the population was insufficiently described
Is the reference standard likely to classify the target condition correctly?	Y, N, U Y if it used selective venography (not MR) of the OV and/or IIV and a definition of PVI was given, N if no definition of PVI was given, U if the definition of PVI was insufficiently described
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Y, N, U Y if there was less than 1 year between tests, N if there was more than 1 year, U if the interval was not stated
Did the whole sample or a random selection of the sample, receive verification using the intended reference standard?	Y, N, U Y if the whole sample had venography, N if only those with evidence of PVI on index test went on to have venography, U if it was not clear or there was suspicion that population was selected retrospectively
Did patients receive the same reference standard irrespective of the index test result?	Y, N, U Y if the same venography methods were used for all, N if different venography was used dependent on the index test, U if it was not clear or there was suspicion of differential verification
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Y, N, U Y if the tests were conducted separately, N if venography was interpreted in light of the index test result, U if it was not clear
Were the reference standard results interpreted without knowledge of the results of the index test?	Y, N, U Y if it was explicitly stated they were interpreted blind to index test, N if venography was undertaken on the basis of index test results, U if it was unclear
Were the index test results interpreted without knowledge of the results of the reference standard?	Y, N, U Y if the index test was used as screening test, N if the study population was retrospectively identified on the basis of reference or index conducted after venography, U if it was not clear
Were uninterpretable/intermediate test results reported?	Y, N, U Y if there was a clear definition of PVI and indeterminate results described, N if there was suspicion that patients were excluded if either test was uninterpretable, U if there was no clear definition of PVI but all patients were apparently accounted for
Were withdrawals from the study explained?	Y, N, U Y if the flow of patients was clear, N if the number undergoing both tests was unexplainably different, U if it was not possible to determine if patients were excluded, e.g. retrospective design

N, no; U, unclear; Y, yes.

Results

Study selection for the review

A total of 6016 citations were identified by the electronic searches. Of these, 12 articles (involving 1579 women) satisfied the inclusion criteria and were included in our review. *Figure 1* shows the flow of studies from identification in the literature searches through to inclusion in the systematic review. A total of 6016 citations were identified from the bibliographic database searches and one citation was found through hand-searching. Of these, 5882 were excluded after screening of titles and abstracts. This left 140 citations for which full-text manuscripts were retrieved. Of these, 128 were excluded, as they were reviews, comments or case reports, they considered the anatomy of pelvic veins in relation to the veins of the lower limbs or there were no usable data. This left 12 studies which fulfilled our inclusion criteria and were included in our review.

Description of study characteristics

Table 6 provides a summary of the characteristics of the studies included in the review. Sample sizes varied from 6 patients to over 1000 in studies exploring the association between lower-limb varicose veins and

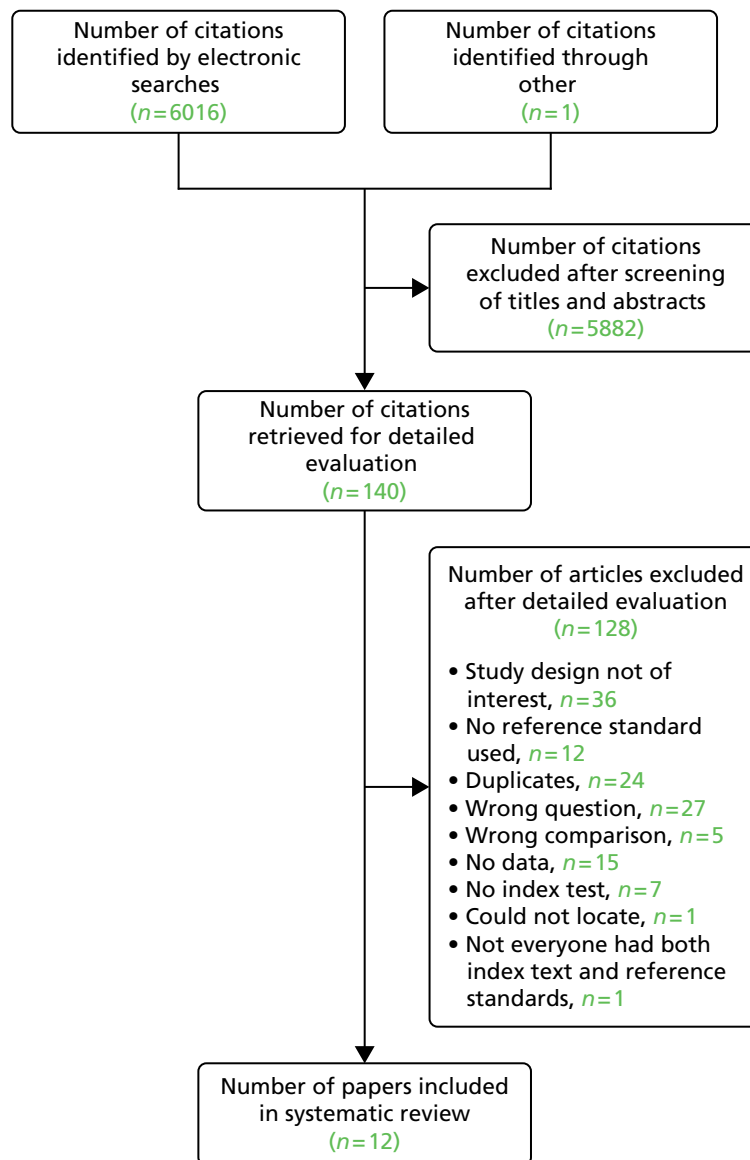


FIGURE 1 Study selection process for the systematic review of the accuracy of non-invasive tests for identification of PVI.

TABLE 6 Characteristics of studies included in the systematic review of the accuracy of non-invasive tests for PVI

Study (author and year)	Primary study aim	Population	Number of patients	Reference standard	Index test(s)
Adams <i>et al.</i> 1987 ⁴¹	Accuracy of ultrasound in relation to venography and laparoscopy	CPP	73	Pelvic venography, no further description	Pelvic ultrasound, no further description
Asciutto <i>et al.</i> 2008 ³⁸	Feasibility and accuracy of MR venography	Suspicion of PVI on clinical history	23	Transcatheter OV and IIV venography, in reverse Trendelenberg position, with Valsalva used	MR venography in supine position, with breath hold
Bachar <i>et al.</i> 2003 ⁴⁴	Assess effectiveness of embolisation	CPP	6	Transcatheter renal vein venography, in supine position, Valsalva used	Doppler ultrasound, presumed transabdominal, position unclear, Valsalva used
Creton <i>et al.</i> 2007 ⁶⁵	Assess effectiveness of embolisation	Suspicion of PVI on clinical history and non-saphenous perineal varicose veins	24	Transcatheter OV and IIV venography, position not stated, Valsalva used	Duplex TAUS in standing position, use of Valsalva not stated
Giacchetto <i>et al.</i> 1990 ⁴²	Comparison of ultrasound and venography	Acyclic pelvic pain with no dysmenorrhoea	35	Transcatheter renal vein venography, position and use of Valsalva not stated	TVUS without Doppler, position and use of Valsalva not stated
Rae <i>et al.</i> 1990 ⁴⁵	Comparison of ultrasound and venography	CPP	30	Transfundal venography, position and use of Valsalva not stated	Duplex TAUS, position and use of Valsalva not stated
Alvi 2013 ³⁶	Assess effectiveness of embolisation	Symptomatic pelvic venous congestion with no further definition	48	Transcatheter venography, position and use of Valsalva not stated	Ultrasound scan, no further description, Dynamic contrast enhanced MRI; position and use of Valsalva not stated
Barros <i>et al.</i> 2010 ³⁷	Determine prevalence and association of varicose veins of lower limb and pelvis by ultrasound and venography	Women undergoing varicose vein screening	1020	Transcatheter renal, OV and IIV venography, position and use of Valsalva not stated	TAUS and TVUS with colour Doppler ultrasound, in supine position Colour Doppler ultrasound of lower limbs, Valsalva used
Carrion Otero <i>et al.</i> 1999 ³⁹	Determine anatomy and physiology of pelvic veins in women with varicose veins	Women undergoing varicose vein screening, with suspicion of PVI	233	Transcatheter renal, OV and IIV venography, position and use of Valsalva not stated	Colour Doppler TVUS, in dorsal position, use of Valsalva not stated
Halligan <i>et al.</i> 2000 ²³	Determine whether or not ultrasound can distinguish between women with and women without CPP	Women with CPP and PVI confirmed by venography	36	Transfundal venography, in supine position, use of Valsalva not stated	Power Doppler TVUS, in supine position, use of Valsalva not stated

TABLE 6 Characteristics of studies included in the systematic review of the accuracy of non-invasive tests for PVI (continued)

Study (author and year)	Primary study aim	Population	Number of patients	Reference standard	Index test(s)
Park <i>et al.</i> 2004 ⁴⁰	Determine whether or not ultrasound can distinguish between women with and women without CPP	CPP with ovarian point tenderness but without other pathology	32	Transcatheter OV venography, in supine position and use of Valsalva not stated	Colour duplex TUAS and TVUS, in supine position, Valsalva used
Yang <i>et al.</i> 2012 ⁴³	Assess accuracy of MR venography	Suspicion of PVI on clinical history	19	Transcatheter OV venography, in supine position, Valsalva used	MR time-resolved venography, position not stated, images captured during shallow breathing

pelvic varicosities. Three studies purported to be assessing the accuracy of ultrasound against venography,^{41,42,45} with a further two being case-control studies of the association of PVI and CPP.^{23,40} Two studies assessed the accuracy of MR venography against conventional venography.^{38,43} Three studies principally reported on the effectiveness of embolisation but included some data on ultrasound as a screening test.^{36,44,65} Two studies looked the relationship between PVI and lower-limb venous insufficiency.^{37,39}

Demographic data on the participants of the selected study are given in *Table 7*. Information was patchy, with some studies not describing their populations. The majority of women were of reproductive age, although in one study the oldest participant was 66 years old. Two of the three case-control studies had

TABLE 7 Demographics of patients in studies of accuracy of non-invasive tests for the determination of PVI

Study (author and year)	Number of patients	Age		Parity		
		Mean (years)	Range (years)	Mean	Range	% nulliparous
Adams <i>et al.</i> 1987 ⁴¹	73	Not stated		Not stated		
Alvi 2013 ³⁶	48	40	23–66	Not stated		
Bachar <i>et al.</i> 2003 ⁴⁴	6	38 (median)	27–53	Not stated	0–5	17%
Creton <i>et al.</i> 2007 ⁶⁵	24	41.5	31–50	2.5 (gravida)	1–4	Not stated
Giacchetto <i>et al.</i> 1990 ⁴²	35	With ovarian reflux 36.1 (SD 7.5); without ovarian reflux 22.5 (SD 4.1)	16–53	Not stated		54%
Rae <i>et al.</i> 1990 ⁴⁵	30	Not stated		Not stated		
Barros <i>et al.</i> 2010 ³⁷	1020	48.1 (SD 14.2)		3.3 (gravida, SD 2.3) for whole population		Not stated
Carrion Otero <i>et al.</i> 1999 ³⁹	233	Not stated	25–53	Not stated		12%
Halligan <i>et al.</i> 2000 ²³	36	29 (median)	22–44	Not stated		
Park <i>et al.</i> 2004 ⁴⁰	Cases 32; controls 35	Cases 39; controls 39	Cases 26–64; controls 27–57	Not stated		
Asciutto <i>et al.</i> 2008 ³⁸	23	51	29–71	Not stated		13%
Yang <i>et al.</i> 2012 ⁴³	19	42	27–61	Not stated		11%

groups who were not comparable in terms of mean age. Information on parity was more scarce, with only 5 out of 11 studies reporting any data on parity. The percentage of nulliparous women included in the studies ranged from 11% to 54%.

Quality assessment

A breakdown of quality items assessed in the 12 included studies is provided in *Table 8*. We considered the possibility of spectrum bias in the two studies recruiting from varicose vein clinics, as patients would not normally be considered for pelvic vein assessment if they did not report CPP. Although all studies used venography as the reference standard, and this appeared to be performed consistently among all those who underwent it, there were three studies that did not adequately define PVI,^{36,37,41} meaning that we could not be clear about whether or not all participants were verified against the same criteria. All but two studies did not describe the interval between the reference standard and index test. The significance of this is unclear, as the natural progression of PVI is unknown. By the nature of the tests, the index and reference tests were performed and interpreted separately.

There was partial verification in five studies, and two further where it was not possible to determine whether all index tests had been verified. In these studies, only those in whom the index test indicated PVI were taken forward to undergo venography. This means that the proportion of false negatives and the sensitivity of the index test cannot be calculated. In these studies, it is implicit that the reference standard is interpreted with knowledge of the index test, and, indeed, only two studies explicitly described blinding, both of which used MR venography. There were a few instances in which a pelvic vein could not be identified by either imaging technique, but this did not necessarily mean an indeterminate response. In the total absence of a flow chart of patients' progression through a study, it is impossible to establish whether or not any women were excluded from the analysis. As some studies were stated as retrospective, it is likely that some selection of patients occurred and the populations were not consecutive.

Accuracy review

Owing to a lack of data within the included studies, it was not possible to generate full 2 × 2 tables for the majority of studies. Therefore, results will be discussed narratively.

Standard ultrasound

The first use of ultrasound in diagnosis came from the same team that produced the seminal paper on the association between PVI and CPP.⁴¹ In this study, 73 women with CPP underwent pelvic ultrasound scans, and pelvic venography was undertaken in 41 of these women. Venography identified varicosities in 33 of the 41 women and ultrasound detected varicosities in 31 of these 33 women, a sensitivity of 94%. It was not possible to compute the specificity. Thirty-two women had laparoscopy and not venography, while 14 women had both venography and laparoscopy. Polycystic ovaries were reported in 44 of the 73 women.

Giacchetto *et al.*⁴² described a study of 35 women in whom there was no pathology that could explain the clinical symptomatology. All women underwent TVUS examination but the proportion in whom dilated veins was observed was not provided. The presence of pelvic varices was confirmed by left OV venography in 16 of 35 women (46%) of cases, and was bilateral in three.

Ultrasound with Doppler

In studies with a focus on embolisation, the description of the diagnostic work-up is poor, and the studies of Bachar *et al.*⁴⁴ and Creton *et al.*⁶⁵ are no exception. Only four patients underwent TAUS and venography in the former⁴⁴ and while PVI was seen in the left OV in three and bilaterally in one immediately before embolisation, the ultrasound findings are not discussed, other than to say that they concurred with venography in failing to see PVI on the right side in the three patients. Creton *et al.*⁶⁵ focused on the anatomical distribution of the ultrasonically identified varices, with all 24 patients exhibiting perineal varices, of which one was bilateral.

TABLE 8 Quality of the studies included in the systematic review of accuracy of non-invasive tests for the detection of PVI

Criteria	Adams <i>et al.</i> 1987 ⁴¹	Alvi 2013 ³⁶	Bachar <i>et al.</i> 2003 ⁴⁴	Creton <i>et al.</i> 2007 ⁶⁵	Giacchetto <i>et al.</i> 1990 ⁴²	Rae <i>et al.</i> 1990 ⁴⁵	Barros <i>et al.</i> 2010 ³⁷	Carrion Otero <i>et al.</i> 1999 ³⁹	Halligan <i>et al.</i> 2000 ²³	Park <i>et al.</i> 2004 ⁴⁰	Asciutto <i>et al.</i> 2008 ³⁸	Yang <i>et al.</i> 2012 ⁴³
Representative spectrum	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y
Appropriate reference standard	U	U	Y	Y	U	Y	Y	Y	Y	Y	Y	Y
Time lag	U	U	U	U	U	U	U	U	U	Y	U	Y
Complete reference verification	N	N	Y	U	Y	Y	N	N	Y	N	Y	Y
Same reference standard	U	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
Independent reference standard	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Blinded reference standard	U	U	U	U	U	U	U	N	U	U	Y	Y
Blinded index test	Y	U	U	U	U	U	U	Y	U	U	Y	Y
Uninterpretable tests reported	U	U	U	U	U	U	U	U	U	U	U	U
Withdrawals explained	U	U	U	U	U	U	U	U	U	U	U	U

N, no; U, unclear; Y, yes.

In an earlier study of 30 women, 23 were confirmed by venography to have PVI, and, while it was stated that there was agreement between TAUS and venography in 22 cases (77%), these cannot be disaggregated, as the description implied that the agreement could be positive or negative.⁴⁵

Carrion Otero *et al.*³⁹ conducted one of the largest studies, recruiting women with lower-limb venous insufficiency and carefully categorising them by their ultrasonic and venographic results. Of the 233 patients, 15 had pelvic veins of < 8 mm by TVUS and were classified as normal and apparently did not undergo venography. In the remainder, five were subsequently reclassified as normal, giving a positive predictive value of 98%.

The population in the study of Halligan *et al.*²³ has been described in *Chapter 4*, but here we are not concerned with the control group. Scoring systems of 3 (normal) to 9 (severe PVI) were described for both venographic and ultrasound observations, but only those 36 with a score of six or more by the venographic score constituted the study population. Using the same threshold for the ultrasound score, a sensitivity of 51% (18 out of 35, with no explanation for the one missing patient) for ultrasound can be deduced, but specificity cannot.²³

Another study, also previously considered in *Chapter 4*, assessed 139 patients with clinical suspicion of PVI who were scanned by both transabdominal and transvaginal approaches. Of those, 74 were described as having pelvic varices without other pathology. Unfortunately, only 32 of these underwent venography, with no rationale as to why only a subset went forward, and so not even a positive predictive value could be computed.⁴⁰

The most comprehensive analysis of the accuracy of ultrasound came from Barros *et al.*³⁷ Pelvic varices were identified in 150 of the 249 patients by TVUS with Doppler and in 156 patients by venography. The diagnostic accuracy parameters of TVUS with Doppler were 96% sensitivity (95% CI 92% to 99%) and 100% specificity (lower 99% CI 97%), with positive and negative predictive values of 100% and 94%, respectively.³⁷

Magnetic resonance venography

Two studies of reasonable quality, albeit small, explored MR venography.^{38,43} The first prospectively recruited women with suspicion of PVI in whom there was no infrainguinal source for lower-limb varices observed on ultrasound.³⁸ MR venography was undertaken in the supine position and venography in the reverse Trendelenburg position, with all images assessed by a single radiologist, blind to the other test and assessed in random order. PVI was defined separately for three anatomical locations: dilated OV of at least 1.5 times the diameter of the contralateral vein, contrast depicting the pelvic plexus or dilatation and tortuosity of the IIV, and graded into three categories of severity.⁹⁰ Images obtained by MR venography were all of satisfactory quality and gave a sensitivity of 88%, 100% and 91% of PVI in the OV, IIV and pelvic plexus, respectively, and corresponding specificity of 67%, 38% and 42%, respectively.

The second study was a retrospective review of 19 premenopausal women who had had both MR and conventional venography on the basis of clinical suspicion of PVI.⁴³ A clear definition for PVI was included, and prompted 16 of the patients to have embolisation following the conventional venography; the remainder did not have the procedure as they were identified as having Nutcracker syndrome. All patients had some degree of reflux, and so the accuracy parameters reflect the ability of MR venography to distinguish grade 1 reflux, which was reflux confined to the left OV and/or parauterine veins, from grade 2, which additionally included reflux in the right OV, both IIVs and varicosities of the vulva and thigh. The MR venography showed excellent agreement between the two independent observers and a sensitivity of 67–75% for MR venography to detect grade 2 reflux. As there were no patients without any reflux, probably due to the retrospective nature of the study, the specificity was unreliably estimated at 100%.

Discussion

Main findings

Transcatheter selective venography performed in a tilted position remains the gold standard for the determination of PVI and is an integral part of pelvic vein embolisation, and so it remains an essential part of the diagnostic process. TVUS with Doppler has a place in the screening of women for pelvic varices, although the data on accuracy are limited. One study provided diagnostic accuracy parameters of 96% sensitivity (95% CI 92% to 99%) and 100% specificity (lower 95% CI 97%), with positive and negative predictive values of 100% and 94%, respectively.³⁷ Similarly, MR venography appears to have good accuracy, but data are limited to one study suggesting 88% sensitivity and 67% specificity for identifying PVI in the OV.³⁸ Imaging modalities that demonstrate both venous dilatation and reflux are necessary.

Strengths and limitations

The strength of this review is the extensive literature search, ensuring that the maximum number of appropriate studies were identified. A quality appraisal of the selected studies was conducted in parallel, and although there are no concerns about the verification method, using venography, it is clear that there are several issues common to most studies that undermine their estimates of accuracy. Only two studies were prospective and included consecutive patients,^{23,38} while in about half, not all of the patients who underwent ultrasound assessment had the findings verified by venography. It was assumed that in order to progress to treatment with embolisation, the venography would have had to confirm the presence of PVI. Invariably, because ultrasound was being used as a triage test to identify those patients who would go on to have venography and embolisation, those who did not show evidence of PVI on ultrasound never had their status verified, and hence specificity cannot be calculated. In these and other studies, another issue was that the venography was performed and analysed with knowledge of the initial test results, which could influence the interpretation. Only the study of Ascitto *et al.*³⁸ was rigorous in its methods to prevent ascertainment bias in the analysis of the images.

Interpretation

The normal appearance of the pelvic venous system is of OVs arising from the ovarian plexus, joining the inferior vena cava on the right side and the left renal vein on the opposite side. Incompetence or absence of veins in the ovarian artery can lead to retrograde flow and progressive dilatation of the vein, creating bulging and tortuous varicosities. For a diagnosis of PVI and potential treatment, the pelvic veins need to be demonstrated not only to be enlarged but also to have poor venous flow; therefore, for identification, a dynamic imaging method is required. Only two studies in our review, both conducted over 15 years ago, used conventional ultrasound.^{41,42} Commentators at that time highlighted the poor sensitivity of this method,¹¹ which is probably due to the restriction a diagnosis of venous incompetence to those with a OV diameter of > 5 mm, missing subtle signs of reflux. We did not locate any direct comparisons between abdominal and vaginal approaches for ultrasound, but intuitively the transvaginal route is likely to give higher-resolution images, particularly for women with high adiposity.

Including a Doppler study in an ultrasound assessment should add significant value to the assessment, and the results of Barros *et al.*³⁷ suggest that this is highly accurate. The ability to assess the Doppler profile during the Valsalva manoeuvre is an important feature. Performing the Valsalva manoeuvre increases intraperitoneal pressure and a variable Doppler waveform is seen. In the context of women with suspected PVI, reversal of flow and an abrupt disappearance of the flow correlate with reflux and stasis seen at venography.⁴⁰ This is a corollary of the use of the Valsalva manoeuvre in the diagnosis of scrotal varicocele in men.⁹¹

The precise technique may be important. Conventional Doppler may be hindered by the tortuous nature of veins, preventing a reproducible placement of the gates on the image, which is not an issue with power Doppler. Vessels with very slow blood flow, as might be expected in situations with enlarged OVAs, are at the limit of the sensitivity of colour Doppler. Power Doppler can provide excellent resolution of the vein wall, and can delineate tortuous veins, but it can also fail to distinguish venous from arterial flow. There are no comparative data for the various Doppler methods, and so this review cannot make any conclusions regarding the most appropriate method, but this may be irrelevant as technology continues to improve the discriminatory power and resolution of images.

Magnetic resonance venography appears to be a very accurate imaging method, and has some advantages. The isotonic nature of the MR contrast agent reduces the risk of thrombosis associated with iodinated contrast as well as reducing the inherent risk of anaphylaxis. MR venography appears to be reproducible, with moderate agreement with conventional venography for anatomical features and a slightly lower agreement for classification of incompetence. CT may also offer similar benefits, but no studies comparing this method with conventional venography were identified. MR venography is apparently highly sensitive in identifying PVI, but, as with laparoscopy, it has compromised specificity owing to the scan being performed in the supine position. The accuracy needs to be confirmed in larger cohorts of well-designed studies but is already becoming widely used.

Chapter 6 Effectiveness of embolisation or sclerotherapy of pelvic veins for reducing chronic pelvic pain: a systematic review

Introduction

Elimination of the blood flow through an incompetent vein is a recognised strategy for incompetent veins. This can be achieved surgically by ligation of a vein or via percutaneous introduction of an embolic agent upstream of the dilated or refluxing veins. Once the incompetent vein is occluded, blood is diverted via other veins and, in time, new vessels can form in the place of the original, although in theory these too could become incompetent. Whether recurrence of symptoms is a result of failure of the original embolisation, through neovascularisation or through untreated or de novo varices, is unclear.

Ligation of OV via open surgery was the first method of achieving occlusion, but subsequently developed into laparoscopic clipping. Improvements in pelvic pain were generally seen, but in the absence of controlled trials, the effectiveness of treatment cannot be determined. With the advent of minimally invasive percutaneous procedures, ligation is generally not offered to women, owing to the added risks and inconvenience of the surgery.

The first case report of transcatheter OV embolisation arose in 1993, when Edwards *et al.*⁹² built on the small series of OV ligation and years of use of embolisation in the management of varicose veins of the leg. They showed that bilateral coil embolisation provided a sustained symptomatic relief to 12 months post procedure.⁹² Since then, the procedure has become the widely used, principal treatment for CPP with demonstrable PVI, and high success rates are often cited.

The technique, usually performed by an interventional radiologist, involves threading a catheter, guided by fluoroscopic imaging, to the OV. Access can be via the groin and femoral vein, or via the jugular vein in the neck. If embolisation is to be performed, small metal coils, absorbable sponges or a sclerosant such as glue or foam are passed through the catheter into the OV. Metal coils are made from stainless steel or platinum, coated with fibres that induce blood clots and approximately 0.9 mm in diameter. Multiple coils can be inserted in the case of lengthy varices. Sclerosants include cyanoacrylate monomers or detergents such as morrhuate sodium, a fatty acid derived from cod liver oil, or sodium tetradecyl sulphate, which is mixed into a foam or slurry. The cyanoacrylate quickly polymerises to form a mechanical obstruction with an exothermic reaction that damages the endothelium, while detergents disrupt the lipids in the endothelial cells, causing an inflammatory response. Both methods ultimately cause the formation of a thrombus and sclerosis of the vein. Once a dilated vein has occluded, the venous blood is diverted via other veins in the pelvic area, for example the IIV, which will also have less turbulent flow from the elimination of the connected refluxing vein.

Objectives

This chapter describes a systematic review of the literature to assess the effectiveness of percutaneous embolisation of pelvic veins in reducing CPP in women. Secondary objectives were to assess radiological features, impact on fertility and adverse events.

Methods

The systematic review was conducted based on a protocol developed prior to commencing the review and registered with the PROSPERO database. The protocol was designed using widely recommended methods for conducting reviews of interventions and is reported in accordance with PRISMA standards.⁹³ Ethics approval was not needed as no patients or identifiable patient data were involved.

Scoping search

A scoping search in PubMed using the term 'pelvic congestion syndrome' retrieved 24 uncontrolled studies involving coil embolisation of pelvic veins and seven studies involved sclerotherapy. Seven studies of OV ligation were identified in an initial scoping search. We made a decision, after registration of the review on the PROSPERO database, to exclude studies of ligation from this review, as this procedure is rarely performed in current practice now that the technically less demanding and lower-risk option of percutaneous vein embolisation is widely available.

Search strategy

A comprehensive search strategy was developed. This was used in the following bibliographic databases: Web of Knowledge, British Nursing Index, CINAHL, The Cochrane Library, DARE, EMBASE, Medion, MEDLINE and Web of Science. The foreign databases AIM, IMEMR, IMSEAR, LILACS, PAHO, Popline, SciELO and WPRIM, held on the World Health Organization portal, were also searched. All databases were searched from database inception to November 2013. Bibliographies of all relevant primary articles and reviews were hand-searched to identify articles missed by the electronic searches. No language restrictions were applied during the searching phase.

Search terms for the condition included 'pelvic pain', 'pelvic congestion', 'pelvic or ovarian vein', 'incompetence or reflux', and variations of these as keywords and text. Search terms for the intervention included 'treatment', 'endovascular therapy', 'interventional radiology', 'embolisation', 'sclerotherapy', 'ligation' and 'occlusion', and variations of these as keywords and text. Wildcard characters were used to capture alternative spellings and stems of words.

The condition and treatments terms were each combined using the 'or' term to broaden the search and the two components were combined using the 'and' function. There was no restriction on study design in the search, based on the output of our scoping search which indicated a dearth of RCTs (see *Appendix 1*).

A comprehensive database was constructed using Reference Manager to store all identified references.

Study selection and data extraction

Studies were selected for inclusion in the review in a three-step process (Figure 2). First, the citations identified by the electronic literature databases searches were screened by one reviewer, who read the titles and abstracts and selected on the basis of the population and intended treatments, and who eliminated all studies that did not appear to describe embolisation or sclerotherapy of pelvic veins. A significant number of citations relating to varicose veins of the leg were anticipated owing to the necessary inclusion of 'iliac vein' as a search term. Any citations referring to treatment of the saphenous vein were excluded, unless the abstract referred to the concurrent treatment of pelvic veins.

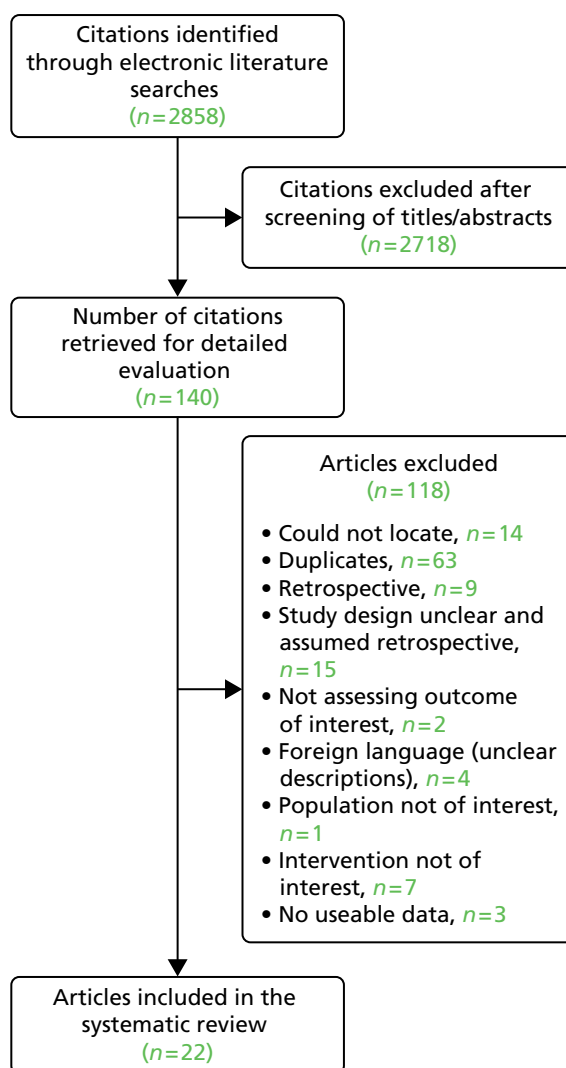


FIGURE 2 Study selection process showing the identification of eligible studies for the review of effectiveness of embolisation.

The second round of screening involved two reviewers, who selected citations that included patients described as having PCS or PVI. Full manuscripts were then retrieved of citations that met or were thought to have met the inclusion criteria. Two reviewers then independently inspected the manuscripts to confirm that the following criteria were fulfilled:

1. Population – women with a clinical diagnosis of PCS and/or radiological diagnosis of PVI, with or without CPP. No restriction was placed on any previous treatment, age of the participants, duration of symptoms, comorbidity (including the copresence of endometriosis or other gynaecological cause) or severity of the complaint in selection of the studies. No restriction was made on the method of identification of the pelvic varices to be embolised.
2. Interventions – coil embolisation or sclerotherapy of pelvic veins. No restriction was placed on the method of embolisation or sclerosant used.
3. Outcomes – the primary objective was to assess the impact of embolisation on pelvic pain, so studies reporting subjective assessment of pain or improvement in pain symptoms were included here. Secondary outcomes were radiological assessments, for example pelvic vein diameter, complication and adverse effects, patient-reported general improvement or quality of life.
4. Study design – ideally, only reports of well-designed RCTs would be included. Preliminary searching indicated that there would be few randomised or well-designed non-randomised controlled studies. Primary reports of observational studies were, therefore, included, but restricted to those in which participants were recruited prospectively. Case reports or small series with fewer than six participants were excluded. Where it was ambiguous whether the data was collected prospectively or retrospectively, a judgement was made based on the time frame of the follow-up assessments. Where participants were reassessed at particular time points, it was assumed that they were recruited into the study prospectively. If the duration of follow-up was reported as a wide time frame, it was assumed that participants had been identified retrospectively and the follow-up was a cross-sectional survey; therefore, these reports were excluded.

Both reviewers extracted data on study characteristics and methods, and noted any limitations described by the authors. Any disagreements surrounding the inclusion of a manuscript were resolved through consensus.

Methodological quality assessment

All manuscripts selected for inclusion were assessed for their methodological quality in duplicate. This was defined as confidence that the study design, conduct and analysis minimised bias in the estimation of effectiveness. For any randomised trials found, the risk of bias tool developed by the Cochrane Collaboration was used.⁹⁴ A randomised study was considered to be of high quality if it provided evidence of adequate randomisation sequence generation and allocation concealment, if blinding was used, if the issue of missing outcome data was adequately addressed and if the published paper was free of selective reporting and other biases.

Acknowledging the lack of RCTs, the quality assessment was redefined for observational case series. These are the least methodologically sound study designs and have inherent problems that can bias causal inference owing to the fundamental problem of a lack of a comparison group. There are no universally accepted quality criteria for case series, as systematic reviews usually tend to exclude studies of this design, and there are no reporting standards. The quality of case series was assessed by considering the following criteria, adapted from a published checklist,⁹⁵ such as they were reported, described in *Table 9*.

TABLE 9 Quality checklist for case series of pelvic vein embolisation

Criteria	Decision
Was the aim of the series to assess the effectiveness of embolisation explicitly stated?	Y, N
Did the study recruit participants prospectively and consecutively?	Y, N, U U if the study stated a retrospective analysis of prospectively collected data
Was it a multicentre study?	Y, N Y only if two or more hospitals could be identified
Were the eligibility criteria for patients undergoing embolisation explicitly provided?	Y, N, U Anticipating that venography to diagnose of PVI would likely be required for embolisation, were the clinical characteristics that prompted further imaging and investigation stated?
Were participants comparable in terms of pain or PVI severity?	Y, N, U Y if the mean pain/PVI severity was stated and had small variance, N if wide variance, U if baseline values not stated
Were the techniques for embolisation or sclerotherapy precisely described?	Y, N
Were additional interventions clearly reported in the study?	Y, N, U Y if planned second embolisation or varicose vein procedures were stated in the methods section, or the proportion having repeat interventions was clear in the results section, or no further interventions were observed; N if no indication was given; U if there was evidence of second/repeat interventions but not the rate
Are outcome measures clearly defined in the introduction or methods sections?	Y, N, U Y if the intention to capture pain, reflux or improvement was explicitly stated as an outcome, N if no outcomes were proposed in methods section; U if outcomes were implied
Were relevant outcomes appropriately measures with objective or subjective methods? Were they measured before and after embolisation (other than adverse events, etc.)?	Y, N, U Y if pain was scored with a VAS or validated scale, described in methods; N if this was not described; U if this was not described in the methods but was apparently used
Was appropriate statistical tests performed?	Y, N, U, N/A Y if paired <i>t</i> -test, McNemar test, etc. was used; N if unpaired tests were used on before-and-after data; U or N/A if there were no variables that could be compared (e.g. only reported improvement)
Were the time points for follow-up clearly reported?	Y, N Y if the methods section described when outcomes were measured
Was the loss to follow-up reported?	Y, U Y if losses were cited or complete follow-up was confirmed; U if it was not clear whether outcomes were collected on all

continued

TABLE 9 Quality checklist for case series of pelvic vein embolisation (*continued*)

Criteria	Decision
Does the study provide estimates of the variability in the analysis of the relevant outcome measures? For example, the SD around a pain score	Y, N, N/A Y when continuous measures were reported with a SD or range; N when they were not; N/A where no continuous variables were reported
Are adverse events reported, or the absence of adverse events acknowledged?	Y, N
Are the conclusions supported by the results?	Y, N, U
Are any competing interests reported?	N, none, conflict N where there was no disclosure of competing interest statement; none where there was a disclosure statement and no conflicts were explicitly described; conflict if it was industry funded

N/A, not applicable; N, no; U, unclear; VAS, visual analogue scale; Y, yes.

Data synthesis

Standard meta-analysis methods were to be used to estimate the overall proportion with a symptomatic improvement following embolisation, using the proportions reported in individual studies and under fixed- and random-effects assumptions. MedCalc software (version 14.10.2, Ostend, Belgium) uses a Freeman–Tukey transformation⁹⁶ to calculate the weighted summary proportion under the fixed- and random-effects model.⁹⁷ Plots were generated in MedCalc. For other outcomes, studies were extracted in duplicate, tabulated and described narratively.

Results

Studies selected for the review

A total of 2858 citations were identified through the electronic bibliographic database searches. Of these, 2718 were excluded after the titles and abstracts were read, mainly because they referred to varicose veins of the lower limbs. This left 140 citations for which full papers were retrieved.

Nine were eliminated, as they were retrospective in design. If there was ambiguity regarding whether the study was prospective or retrospective, and it was available only as an abstract, the citation was excluded. Four studies, in non-English journals, had limited translation which indicated wide follow-up time periods, and were excluded on the assumption that they were retrospective in design.

Seven studies where pelvic vein ligation was investigated were identified. The original objective had been to include such studies in the review and search terms relating to pelvic vein ligation were retained in the search strategy to maximise the retrieval of studies of intervention. Of the seven studies, one was a case report of a single procedure, two were in Chinese, one reported on open procedures that are no longer practised and one was a study of female kidney donors and the association between pelvic varices and CPP. The remaining two studies considered more appropriate laparoscopic pelvic vein ligation, reporting on 50 patients in total, with one study making a non-randomised comparison against medical treatment.

Three studies were excluded at the final stage because they were considered retrospective, but as they reported on medium- to long-term outcomes they were considered for this outcome.^{62,98,99} Two studies, with a total of 37 patients, although prospective in design, reported only on technical success and complications, and so were excluded.^{100,101} This left 22 studies, reporting on 1308 patients.^{15,31,46–65} A summary of the characteristics of the included studies is given in *Table 10*.

TABLE 10 Characteristics of studies selected for inclusion in systematic review of effectiveness of embolisation of PVI

Author, date and country	Number	Patient group	Treatment	Study type	Outcomes, follow-up period	Key results
Capasso <i>et al.</i> 1997, Belgium ⁶³	19	Women with clinical and ultrasonographic or radiological evidence of PVI	OV vein glue ($n = 24$), coil ($n = 2$) or combined ($n = 4$) embolisation; left OV only $n = 13$, bilateral $n = 6$	Prospective observational study	Subjective assessment of pain relief within 4 weeks. Transabdominal Doppler ultrasound at 5 weeks. Average 15-month follow-up for recurrence	Early outcomes: 74% had improvements in pain symptoms (complete relief in 58%, partial in 16%). Improvement correlated with ultrasonographic evidence of complete thrombosis of varices. Dyspareunia ($n = 5$) persisted. $n = 5$ with persistent pain had reintervention. Two venous perforations that resolved
Tarazov <i>et al.</i> 1997, Russia ⁵⁷	6	Women with clinical and radiological evidence of PVI	Bilateral $n = 1$ or left unilateral $n = 5$ OV coil embolisation	Not stated	Subjective reporting of symptom improvement; follow-up duration 1–4 years	Complete alleviation of CPP in all women within 4 weeks. Improved menstrual symptoms in 2 women with dysmenorrhoea. No serious complications
Cordts <i>et al.</i> 1998, USA ⁵⁸	9	Women with clinical and ultrasonographic and/or radiological evidence of PVI	Bilateral $n = 4$ or left unilateral $n = 4$ OV coil embolisation	Consecutive case series	Numerical rating scale of symptom relief, mean follow-up 13 months	Eight women (88.9%) had > 80% immediate symptom relief. Two women had a mild or moderate return of the symptoms at 6 and 22 months, respectively. One lower lobe coil pulmonary embolus
Scultetus <i>et al.</i> 2002, USA ⁵³	15 (treated with sclerotherapy)	Women with 'mild' discomfort, small varices and mild reflux by Doppler ultrasound	Sclerotherapy of varices alone or with excision of varices	Prospective observational study	VAS of improvement. Mean follow-up 2.3 years	Twelve had excellent improvement and three had moderate improvement. No deep-vein thrombosis reported
Venbrux <i>et al.</i> 2002, USA ⁶⁴	56	Women with clinical and ultrasonographic and/or radiological evidence of PVI	Bilateral OV (100%) and subsequent IIV (77%) coil embolisation	Prospective observational study	VAS for pain, menstrual cycle questionnaire at 3, 6 and 12 months post procedure	Mean pain 7.8 at baseline decreased to 4.2 at 3 months, 3.8 at 6 months and 2.7 at 12 months ($p < 0.001$ for all comparisons). No significant changes in cycle length

continued

TABLE 10 Characteristics of studies selected for inclusion in systematic review of effectiveness of embolisation of PVI (continued)

Author, date and country	Number	Patient group	Treatment	Study type	Outcomes, follow-up period	Key results
Chung and Huh 2003, South Korea ³¹	106, of whom 52 treated with embolisation	Pre-menopausal women with idiopathic CPP and a score of ≥ 5 on a modified venography scale, refractory to MPA	(a) OV or IIV coil embolisation (n = 52); (b) hysterectomy with bilateral oophorectomy (n = 27); (c) hysterectomy with unilateral oophorectomy (n = 27)	RCT	VAS at 3, 6, and 12 months post procedure, patient global impression of change	Statistically significant decrease from baseline and between embolisation and hysterectomy groups at all time points
Pieri <i>et al.</i> 2003, Italy ⁵⁹	33	Women with clinical and ultrasonographic evidence of PVI	OV foam sclerotherapy (64% bilaterally)	Prospective observational study	Subjective rating of various pain symptoms at 1 month. Clinical assessment and mean venous diameter by ultrasound at 6 months	Improvement in pain in 61%. Mean OV diameter at baseline: right 4.5 mm and left 6.3 mm, reduced to 3.10 mm and 4.4 mm, respectively, at follow-up. Seven patients had transient flank pain
Kim <i>et al.</i> 2006, USA ¹⁵	127	Women with clinical and radiological evidence of PVI, including 25 with hysterectomy	Bilateral (85%) or unilateral (15%) OV coil/sclerosant embolisation, with 85% having subsequent IIV sclerosant embolisation	Retrospectively identified women followed up prospectively	VAS and composite clinical assessment at 3 and 6 months and annually thereafter	Mean pelvic pain at baseline 7.6 (SD 1.8) and 2.9 (SD 2.8) ($p < 0.0001$) and 80% had significant improvement at mean 45 months' follow-up. All pain symptoms significantly improved. Two coil migrations
Leal Monedero <i>et al.</i> 2006, Spain ⁵⁵	239	Women with clinical and radiological evidence of PVI (with or without CPP) and lower-limb VV	Coil embolisation with or without foam, of OV or IIV, with VV surgery where indicated	Observational study (unclear whether prospective or retrospective)	Clinical assessment at 6 months post procedure	Complete resolution of pain symptoms in 120 out of 239 (50.2%) and partial relief in 95 out of 239 (36.8%). Superficial phlebitis at point of venous access in 21 patients. No coil migrations

Author, date and country	Number	Patient group	Treatment	Study type	Outcomes, follow-up period	Key results
Richardson and Driver 2006, Australia ⁵⁴	26	Women with CPP and ultrasonographic evidence of PVI	Coil embolisation, with or without foam, of OV	Case series, with historical control group undergoing OV ligation. Patient information suggests prospective	VAS for pain symptoms and patient overall satisfaction. Mean follow-up 22 ± 13 months	No significant difference between groups in demographics and presenting symptoms. Coil group pain score statistically significantly reduced from 6.6 (SD 1.9) to 4.0 (SD 2.8), from baseline. No statistically significant difference in pain reduction between ligation and embolisation groups or in overall satisfaction. No coil migration within 6 weeks; one coil perforation detected at 5 months
Creton <i>et al.</i> 2007, France ⁵⁵	24	Pre-menopausal women with dysmenorrhoea/dyspareunia and radiological evidence of PVI	OV or IIV coil embolisation	Prospective observational study	VAS for dysmenorrhoea, dyspareunia and venous pain (individually and total); clinical assessment at 45 days' and 1, 2 and 3 years' follow-up	Statistically significant decreases in all three pain symptoms and improvements in clinical assessment maintained. One coil migration
Greiner and Gilling-Smith 2007, France ⁴⁵	13 (of 24 embolised)	Women with clinical and ultrasonographic evidence of PVI with CPP and lower-limb VV	Bilateral and unilateral coil or glue or combined embolisation of OV and IIV	Observational study (assumed prospective)	Repeat TVUS at 1 and 6 months, 1 and 4 years. Repeat clinical assessment and venography at 4 years	Complete resolution of symptoms in 10/13 and significant improvement in 3/13. No recurrence of PVI
Kwon <i>et al.</i> 2007, South Korea ⁶⁰	67	Women with clinical and radiological evidence of PVI	OV coil embolisation (96% left OV only)	Prospective study of outcome with baseline pain determined by telephone interview or medical note review	Categorical pain severity scale. Mean follow-up 45 months	82% reported total or significant pain reduction. Two coil migrations
Gandini <i>et al.</i> 2008, Italy ⁵⁶	38	Women with CPP and ultrasonographic evidence of PVI	Bilateral OV foam sclerotherapy (3% STSF)	Described as retrospective but included all patients at three defined time points	VAS for four pain symptoms at 1, 3, 6 and 12 months' follow-up	Mean VAS for CPP showed decrease from 7.8 (SD 1.8) to 2.7 (SD 2.8), from 4.9 (SD 4.2) to 2.2 (3.1) for menstrual pain, from 3.3 (SD 3.7) to 1.5 (SD 2.7) for dyspareunia and 3.5 (SD 3.9) to 1.5 (SD 3.0) for urinary urgency at 12 months, all statistically significant

continued

TABLE 10 Characteristics of studies selected for inclusion in systematic review of effectiveness of embolisation of PVI (continued)

Author, date and country	Number	Patient group	Treatment	Study type	Outcomes, follow-up period	Key results
Ratnam <i>et al.</i> 2008, UK ⁴⁷	218	Women with ultrasonographic evidence of PVI and veins communicating with lower-limb VV	Bilateral and unilateral coil embolisation of OV and IIV, with VV surgery deferred to > 8 weeks post procedure	Prospective inclusion, retrospective data extraction from medical notes	Repeat TVUS at 6–8 weeks	Of 193 with follow-up, 16 had residual mild reflux, six had marked reflux and three had new reflux Two coil migrations, one misplacement, one case of perineal thrombophlebitis
Sukovatkh <i>et al.</i> 2008, Russia ⁴⁸	59	Women with clinical and ultrasonographic and/or radiological evidence of PVI	Sclerotherapy	Not stated	Clinical examination, USS and self-reported quality of life	Improvements (not defined) were classified as excellent in 32.6%, good in 46.1%, satisfactory in 19.1% and unsatisfactory in 2.2% of the patients
Tropeano <i>et al.</i> 2008, Italy ⁵²	20	Women with CPP and ultrasonographic evidence of PVI, with no pelvic pathology seen at laparoscopy and embolisation possible anatomically	Sclerotherapy of the OV (15% bilateral)	Prospective observational study	VAS for pain, menstrual cycle questionnaire and ultrasound at 3, 6 and 12 months post procedure	Three women had repeat embolisation after 3 months owing to no change in symptoms and residual PVI on ultrasound. 17 (85%) achieved marked to complete relief until 6 months, with two describing a reduction in relief by 12 months Median VAS pain scores decreased from at 8.0 (range 6.0–10.0) at baseline to 2.0 (range 1.0–5.0), 2.5 (range 1.5–5.0) and 3.0 (range 2.0–6.0) at 3, 6 and 12 months, respectively, all statistical significantly reductions ($p < 0.001$)
Asciutto <i>et al.</i> 2009, Germany ⁴⁹	35 (26 also had concurrent VV surgery)	Women with clinical and radiological evidence of PVI	OV ($n = 28$), IIV ($n = 5$) or both ($n = 2$) with coil embolisation	Prospective observational study	VAS of pain at 1, 2 and 3 years' follow-up	VAS scores for isolated OVI: baseline mean 5.2 (SD 3.5) and 1.2 (SD 0.9) at 3 years; $p < 0.0001$, non-statistically significant reduction for combined OVI and IIV or isolated IIV alone. At mean follow-up of 45 months, overall 47% had sustained improvement. Three venous perforations that resolved
D'Archembeau <i>et al.</i> 2010, Belgium ⁶²	193 (130 had PVI)	Women with clinical and radiological evidence of PVI	Bilateral (4.7%) or unilateral coil (94.3% left, 1% right) coil embolisation of OV	Prospective observational study	Symptom rating on VAS before procedure and at 1 year	11 (5.7%) were re-embolised between 3 months and 6 years. Out of 102 patients with PCS symptoms, 91 (89.2%) reported improvement in symptoms on VAS

Author, date and country	Number	Patient group	Treatment	Study type	Outcomes, follow-up period	Key results
Tinelli <i>et al.</i> 2012, Italy ⁶¹	28	Women with ultrasonographic and radiological evidence of PVI	OV foam sclerotherapy (29% bilaterally)	Not started but follow-up at specific time points	VAS for pain, clinical examination and USS at 10 days, 1 and 6 months post procedure	At 1 month, 6 (21%) reported PVI symptoms, which resolved by 6 months. Reduction in varicosity size from 6.9 mm (SD 2.1 mm) on left and 5.1 mm (SD 1.4 mm) on right to < 4.5 mm in all embolised veins. 100% technical success with no adverse events beyond minor analgesics needs in six (21%) patients
van der Vleuten <i>et al.</i> 2012, Netherlands ²⁰	21 who responded follow-up survey	Women with CPP and radiological evidence of PVI with or without lower-limb VV	Bilateral or unilateral sclerotherapy of OV	Prospective observation study for 2-month follow-up, with cross sectional follow-up at mean 18 ± 122 months	5-point ordinal scale of eight pain symptoms and pelvic varices and haemorrhoids, and global impression of change	14 (66.7%) and 16 (76.2%) women had moderate or obvious improvement or no symptoms, at 2 months and at the survey, respectively. All pain symptoms except backache or urinary symptoms showed statistically significant improvements. Nine (42.9%) women had a second embolisation
Meneses <i>et al.</i> 2013, Chile ⁵¹	10	Women undergoing repeat surgery for VV recurrence and clinical and radiological evidence of PVI	Combined OV and/or IIV embolisation, using sodium morrhuate sclerosant and coil	Prospective observational study	VCSS and VAS for pain at 3 months' follow-up	Significant decrease in pain from 8.2 at baseline to 4.0 at 3 months ($p < 0.001$). Significant decrease in VVCS from 8.4 at baseline to 3.6 at 3 months' follow-up ($p < 0.001$). No VV recurrence by 6 months

STSF, sodium tetradecyl sulphate foam; USS, ultrasound scan; VAS, visual analogue scale; VCSS, Venous Clinical Severity Scale; VV, varicose veins.

Description of study characteristics

The mean age of the study population was reported in 20 of the studies and ranged between 32 and 51 years, with the minimum age of those treated being 19 years and the maximum age being 72 years (Table 11).^{15,31,46,47,49–54,56–65} Only one study appeared to put an age limit on study inclusion,⁴⁸ although tacit age restrictions may have been applied in other populations but not reported. Sixteen studies reported the reproductive status of the treated women in some format, usually as the mean parity, which ranged from 0.9 to 3.5.^{31,46,47,49–54,56–58,60,61,63,65} Five studies clearly did not include any nulliparous women,^{46,51,53,65,66} whereas in the study by Tropeano *et al.*⁵² nearly half of patients were nulliparous. There was no consistent reporting of any other demographic data, such as body mass index, or of history, such as the duration of symptoms.

TABLE 11 Demographics details of the patients in the included studies of effectiveness of embolisation

Author and date	Age (years)			Parity (gravida)			% nulliparous
	Mean	SD	Range	Mean	SD	Range	
Capasso <i>et al.</i> 1997 ⁶³	35.2	NS	24–59	2 (2) ^a	NS	0 (0) to 5 (6)	22.2
Tarazov <i>et al.</i> 1997 ⁵⁷	32.5	6.3	25–40	1.2 (6.5)	NS	0 (4) to 2 (9)	16.6
Cordts <i>et al.</i> 1998 ⁵⁸	32.2	6.5	20–43	> 2 (> 2)	NS	NS	0
^b Scultetus <i>et al.</i> 2002 ⁵³	34	NS	24–48	(3.1)	NS	2 to 5	NS
Venbrux <i>et al.</i> 2002 ⁶⁴	32.3	NS	16–66	NS	NS	NS	NS
Chung and Huh 2003 ³¹	40.1	4.9	NS	2.1	1.1	NS	7.7
Pieri <i>et al.</i> 2003 ⁵⁹	44.3	NS	36–56	NS	NS	NS	NS
Kim <i>et al.</i> 2006 ¹⁵	34	12.5	NS	NS	NS	NS	NS
Leal Monedero <i>et al.</i> 2006 ⁵⁵	NS	NS	NS	NS	NS	NS	NS
^b Richardson and Driver 2006 ⁵⁴	37.5	6.9	NS	3.3	1.2	NS	NS
Creton <i>et al.</i> 2007 ⁶⁵	41.5	NS	31–50	NS (2.5)	NS	(1 to 4)	NS
Greiner and Gilling-Smith 2007 ⁴⁶	41	NS	32–65	4	NS	2 (2) to 8 (8)	0
Kwon <i>et al.</i> 2007 ⁶⁰	39.1	9	25–64	2.4	NS	NS	0
Gandini <i>et al.</i> 2008 ⁵⁶	36.9	NS	22–44	NS	NS	NS	13.1
^c Ratnam <i>et al.</i> 2008 ⁴⁷	46.3	NS	28–70	NS	NS	NS	3.3
Sukovatykh <i>et al.</i> 2008 ⁴⁸	NS	NS	NS	NS	NS	NS	NS
Tropeano <i>et al.</i> 2008 ⁵²	36	NS	19–50	0.9 (0.9)	0.9	0 to 2	46
Asciutto <i>et al.</i> 2009 ⁴⁹	49	11	27–72	NS (2.5)	NS	0 to 7	NS
D'Archambeau <i>et al.</i> 2010 ⁶²	40.3	NS	20–66	NS	NS	NS	NS
Tinelli <i>et al.</i> 2012 ⁶¹	51	NS	43–59	2.1	NS	NS	NS
van der Vleuten <i>et al.</i> 2012 ⁵⁰	41.7	9.6	30–71	2.9	1.1	2 to 6	NS
Meneses <i>et al.</i> 2013 ⁵¹	38	NS	25–39	3.5	NS	2 to 5	NS

NS, non-significant.

a Described as mean parity and gravida in 15 parous women of the 19 in study.

b Data for whole reported population, not solely for those undergoing embolisation.

c Data recorded only for first 60 patients of 218 in study.

Bilateral embolisation was conducted on 478 women, while 384 had only left-side embolisation and six only had right-side embolisation. For the remaining 439 women, it was unclear whether unilateral or bilateral embolisation had been performed. The total number of veins embolised was also unclear, as the procedure was frequently reported as being performed on all incompetent veins including adjacent branches. Furthermore, the number or proportion of women who had the OV or IIV embolised is undeterminable. One of the larger series of 218 women⁴⁷ reported the distribution of the 526 veins treated as 27% right IIV, 23% left IIV, 7% right OV and 32% left OV, but the degree of multiple vein embolisation could not be extracted from the study report.

Embolisation of pelvic veins was achieved using a sclerosant in 229 patients, by the use of metal coils (stainless steel or platinum) in 660 patients and by a combination of both in 405 patients, with the method unclear in the remaining 13 patients. The sclerosant used varied considerably and included 1–3% sodium tetradecyl sulphate,^{53,56,59,102} 2–3% aetoxisclerol^{46,52,55,61,66} or enbucrilate.^{50,63} There was no apparent trend towards or away from using either technique, either over time or between countries.

Quality assessment

There were 20 case series included in the review (Table 12), with one unable to be reliably assessed owing to uncertainty after its translation.⁴⁸ Although the aims and embolisation techniques were clearly stated, one-third did not clearly describe the intended outcome measures and how they were to be collected. Although we sought only prospective trials, it was still not clear in 40% that consecutive patients were included; this was reinforced by poor descriptions of the criteria used to refer patients for venography and inadequate reporting of losses to follow-up. All but one⁶¹ were single-institution studies, but none reported conflicts of interest or funding from interventional radiology companies.

Poor reporting hindered the assessment of the risk of bias in the sole randomised trial, but this was likely to have been subject to selection, performance, measurement and attrition biases. The trial compared embolisation with hysterectomy with bilateral or unilateral oophorectomy and, therefore, could not be blinded. The randomisation and allocation concealment method were inadequately described and produced unequal groups, from which there were substantial exclusions from the hysterectomy groups. Overall, the trial was deemed of low internal validity.

Symptomatic improvement

Subjective symptom relief was reported on ordinal scales of complete, moderate/partial and no relief of CPP symptoms in six studies,^{48,50,53,57,58,63} four of which were definitely prospectively recruited.^{50,53,58,63} Early reporting of complete symptom relief, < 2 months, ranged from 33%⁴⁸ to 80%⁵³ of study participants. Cordts *et al.*⁵⁸ found that 89% of women reported a greater than 80% immediate improvement, although the time scale was not defined, while all six participants in the study by Tarazov *et al.*⁵⁷ reported complete resolution of symptoms at 4 weeks.

Pooling rates of complete, excellent or moderate improvement from these studies gave an overall rate of 75% (95% CI 64% to 85%, $I^2 = 42%$) at 4–8 weeks post procedure (Figure 3).

Few studies reported symptom at two time points. van der Vleuten *et al.*⁵⁰ assessed all women twice and found that 67% of women had moderate or obvious improvement at 2 months postoperatively, a figure that increased to 76% at an average of 18 months (± 12 months) later. Other studies reported that 85% of women had some symptom improvement at 6 months,^{52,55} which in the smaller study increased to 95% after 12 months. At an average of 45 months' follow-up, relief rates of over 80% were reported by two studies^{15,60} but in a third study sustained relief was reported in only 47% of patients.⁴⁹

Studies reported treatment failures as residual symptoms, as unsatisfactory improvement or as the number of repeat embolisations performed. In a larger study, 22 out of 193 (11%) of women had mild or moderate residual symptoms at 6 weeks,⁴⁷ while another reported that only 2.2% found their improvement unsatisfactory.⁴⁸

TABLE 12 Quality assessment of case series included in the systematic review of effectiveness of embolisation for PCS

Study	1: aim	2: prospective	3: multi-centre	4: eligibility	5: comparable pain at baseline	6: technique	7: other interventions
Capasso <i>et al.</i> 1997 ⁵³	Y	U	N	N	U	Y	Y
Tarazov <i>et al.</i> 1997 ⁵⁷	Y	U	N	N	Y	Y	N
Cordts <i>et al.</i> 1998 ⁵⁸	Y	Y	N	N	Y	Y	Y
Scultetus <i>et al.</i> 2002 ⁵³	Y	U	U	N	Y	Y	U
Venbrux <i>et al.</i> 2002 ⁶⁴	Y	Y	U	N	U	Y	Y
Pieri <i>et al.</i> 2003 ⁵⁹	Y	U	N	N	U	Y	Y
Kim <i>et al.</i> 2006 ¹⁵	Y	Y	N	N	U	Y	Y
Leal Monedero <i>et al.</i> 2006 ⁵⁵	Y	U	N	Y	U	Y	Y
Richardson and Driver 2006 ⁵⁴	Y	Y	N	N	U	Y	U
Creton <i>et al.</i> 2007 ⁵⁵	Y	Y	N	Y	Y	Y	Y
Greiner and Gilling-Smith 2007 ⁴⁶	Y	Y	N	N	U	Y	Y
Kwon <i>et al.</i> 2007 ⁶⁰	Y	U	N	N	N	Y	Y
Gandini <i>et al.</i> 2008 ⁵⁶	Y	N	N	N	Y	Y	Y
Ratnam <i>et al.</i> 2008 ⁴⁷	Y	Y	N	N	U	Y	Y
Tropeano <i>et al.</i> 2008 ⁵²	Y	Y	N	N	N	Y	Y
Asciutto <i>et al.</i> 2009 ⁴⁹	Y	Y	N	Y	U	N	Y
D'Archangeau <i>et al.</i> 2010 ⁶²	Y	Y	U	U	U	Y	U
Tinelli <i>et al.</i> 2012 ⁶¹	Y	U	Y	Y	Y	Y	Y
van der Vleuten <i>et al.</i> 2012 ⁵⁰	Y	Y	N	N	U	Y	Y
Meneses <i>et al.</i> 2013 ⁵¹	Y	Y	N	Y	Y	Y	Y

N/A, not applicable; N, no; U, unclear; Y, yes.

8: outcomes described	9: valid outcome	10: statistics	11: time points	12: loss to follow-up	13: variability	14: adverse events	15: conclusions	16: conflicts
N	N	N/A	N	U	N/A	Y	Y	N
N	N	N/A	Y	U	N/A	Y	Y	N
U	U	N/A	N	U	N/A	Y	Y	N
Y	U	N	N	Y	N/A	Y	U	N
Y	Y	Y	Y	Y	Y	Y	Y	N
N	N	N	Y	U	N/A	Y	U	N
Y	Y	Y	Y	Y	Y	Y	Y	None
N	N	N	N	U	N/A	N	Y	N
Y	Y	Y	N	U	Y	Y	Y	N
Y	Y	Y	Y	Y	N/A	Y	Y	N
Y	Y	N/A	Y	Y	N	Y	Y	N
Y	Y	N/A	Y	Y	N	Y	Y	N
Y	Y	Y	Y	U	Y	Y	Y	N
N	N	N	Y	Y	N/A	Y	Y	N
Y	Y	Y	Y	Y	Y	Y	Y	N
Y	Y	Y	Y	Y	Y	Y	Y	None
Y	Y	U	Y	Y	N/A	N	Y	N
Y	U	U	Y	U	Y	Y	Y	N
Y	Y	Y	Y	Y	Y	N	Y	None
Y	Y	Y	Y	U	Y	Y	Y	N

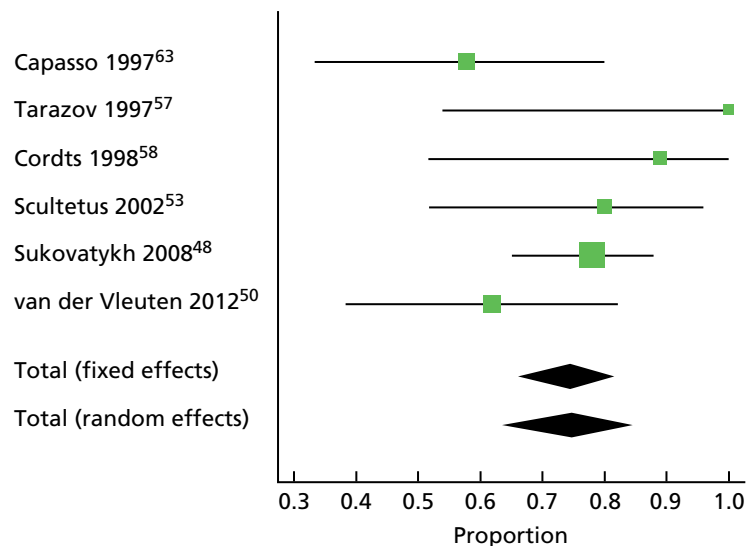


FIGURE 3 Meta-analysis of rates of complete, excellent or moderate improvement 4–8 weeks following embolisation.

D’Archambeau *et al.*⁶² reported reintervention by 3–6 months owing to unresolved symptoms in 5.7% of patients, a figure lower than the 15% at 3 months cited by Tropeano *et al.*⁵² There were two repeat embolisations at 6 and 22 months noted in a study of just nine patients,⁵⁸ while Capasso *et al.*⁶³ reported that 5 of 19 patients (26%) underwent repeat embolisations at an average of 15 months.

No study reported quality of life using a generic instrument. Chung and Huh deployed a social readjustment rating scale¹⁰³ to compare stress between women who had embolisation and those who had hysterectomy, but found no significant differences.³¹

Pain scores

Nine studies report on pelvic pain scores using 0- to 10-cm visual analogue scales, although at varying time points after embolisation.^{15,31,38,50–52,59,64} The mean pain score was reported in all but one study,⁵² which reported the median score, and five studies reported a SD around the mean. In all cases, the pain score reduced significantly from a baseline of about 5 to 8 points to between 1 and 4.2 points at 3 months, or between 1.2 and 3 points at 12 months.

Five studies undertook paired *t*-tests of pain scores before and after embolisation and reported the reductions as being statistically significant, with sufficient data to allow verification by the reviewers.^{15,49,51,54,56} Not enough studies had all of the necessary data to allow a meta-analysis to be performed (*Table 13*).

The decreases were generally sustained in those trials that reported multiple time points (*Figure 4*).

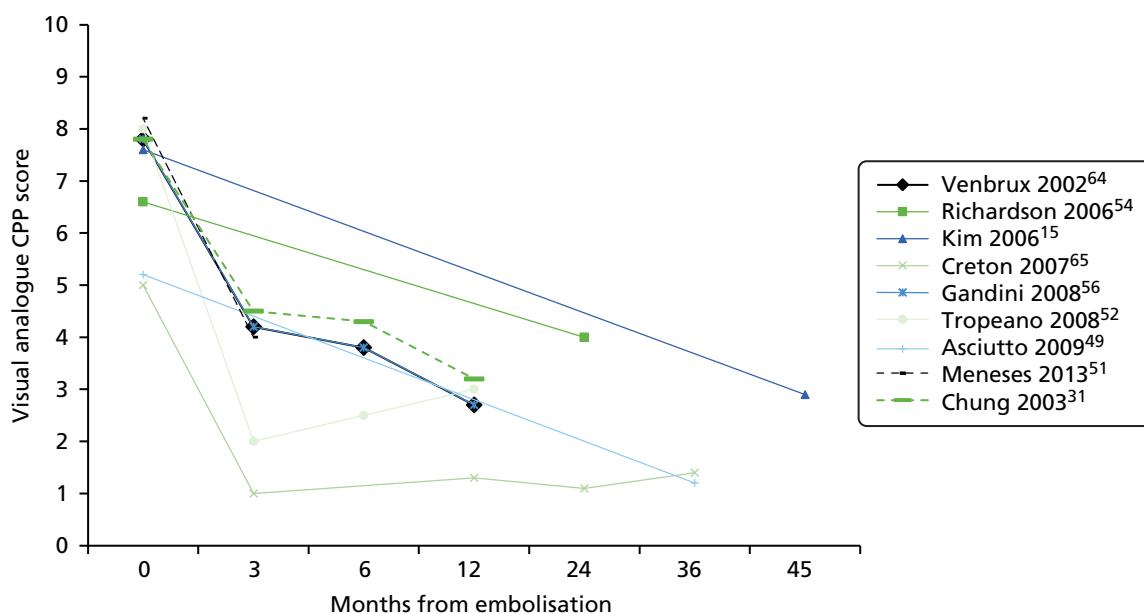
Several studies reported on different pain symptoms. Kim *et al.*¹⁵ noted statistically significant score reductions in pain on standing, lying down, dyspareunia and dysmenorrhoea, as well as a reduction in urinary frequency and the amount of pain relief required, while Venbrux *et al.*⁶⁴ also observed similar reductions in all symptoms except dysmenorrhoea. Gandini *et al.*⁵⁶ reported statistically significant reductions in dyspareunia, dysmenorrhoea and urinary frequency; Creton *et al.*⁶⁵ also considered pain at the site of pelvic varices occurring specifically before or during menstruation, which decreased from a mean of 6.0 to 1.7 at 45 days post embolisation and remained low. van der Vleuten *et al.*⁵⁰ reported on the widest range of symptoms, observing statistically significant improvements in scores at 2 months and an average of 18 months (SD 12 months) for dysmenorrhoea, dyspareunia, worsening of symptoms with walking, standing or sitting, varicose veins and pain in varicose veins. Haemorrhoids improved significantly over long-term follow-up; however, no improvements were seen for urinary symptoms or backache. A composite score of all

TABLE 13 Pain scores before and after embolisation of PVI

Study	Time point (months)						
	0	3	6	12	24	36	45
Venbrux <i>et al.</i> 2002 ⁶⁴	7.8	4.2 ^a	3.8 ^a	2.7 ^a			
Chung and Huh 2003 ³¹	7.8 (1.2)	4.5 (0.9) ^b	4.3(0.8) ^b	3.2 (0.9) ^b			
Kim <i>et al.</i> 2006 ¹⁵	7.6 (1.8)						2.9 (2.8) ^c
Richardson and Driver 2006 ⁵⁴	6.6 (1.9)				4.0 (2.8) ^d		
Creton <i>et al.</i> 2007 ⁶⁵	5.0	1.0 ^d		1.3 ^d	1.1 ^d	1.4 ^d	
Gandini <i>et al.</i> 2008 ⁵⁶	7.8 (1.8)	4.2 (1.9) ^b	3.8 (0.9) ^b	2.7 (2.8) ^b			
Tropeano <i>et al.</i> 2008 ⁵²	8 ^{a,e}	2 ^{a,e}	2.5 ^{a,e}	3 ^{a,e}			
Asciutto <i>et al.</i> 2009 ⁴⁹	5.2 (3.5)			2.1	1.5	1.2 (0.9) ^c	
Meneses <i>et al.</i> 2013 ⁵¹	8.2 (0.9)	4.0 (1.7) ^d					

a $p < 0.01$.b $p < 0.05$.c $p < 0.0001$.d $p < 0.001$.

e Median.

 p -values are compared with baseline, as reported.**FIGURE 4** Time course of pain scores following embolisation for PVI.

10 symptoms, each ranked for severity at baseline and improvement at follow-up, from 1 (no complaints) to 5 (many complaints/worsening), was derived. The mean score improved from 26 before embolisation to 21 at 2 months and 19 at the long-term time point, both statistically significant decreases from baseline.

Impact on the pelvic vein reflux and diameter

Only two studies quantified the diameter of the pelvic veins before and after the procedure.^{59,61} One study measured the mean diameter of varices in supine patients, from 6.3 mm to 4.4 mm and from 4.5 mm to 3.1 mm for the left and right OV, respectively, both statistically significant reductions.⁵⁹ In another study, left and right OV diameters reduced from a mean of 6.9 mm (SD 2.1 mm) and 5.1 mm (SD 1.4 mm) to < 4.5 mm on both sides in all cases.⁶² Pieri *et al.*⁵⁹ noted that symptoms persisted in women in whom OV varicosities, although decreased in diameter from pre-procedure measurements, remained > 5 mm at rest.

Ratnam *et al.*⁴⁷ was able to perform a repeat TVUS at 6–8 weeks in 193 patients, observing residual mild reflux in 16 (8.3%). Nine women had a second procedure dictated by the ultrasound: six patients owing to moderate persistent reflux and three because of new reflux. Tropeano *et al.*⁵² also repeated the TVUS at 3, 6 and 12 months and observed an absence of reflux and reduced (< 5 mm) pelvic vein diameter in 17 out of 20 (85%) women. The remaining three patients who showed recurrence or persistent left-sided reflux, and were also those who did not report a symptomatic improvement, had a successful repeat procedure performed at 4–5 months and were reported as symptom free after a median follow-up of 15 months.

Impact on varicose veins of the leg

Meneses *et al.*⁵¹ reported on the impact of pelvic vein embolisation on both pelvic and leg symptoms in women with recurrent varicose veins and clinical and radiological evidence of PVI, using the venous clinical severity score (VCCS).¹⁰⁴ This scale affords four levels (summarised as absent, mild, moderate and severe) to nine criteria (pain, number of varicose veins, venous oedema, pigmentation, inflammation, induration, number, duration and size of active ulcerative lesions) and one therapy criteria (none to continually) to give a 0–30 scale score. The study reported a statistically significant decrease in the VCCS score from 8.4 to 4.0 ($p < 0.001$) after embolisation in its 10 patients.

Impact on future fertility, menstruation and ovarian reserve

Venbrux *et al.*⁶⁴ captured information on menstruation between 6 and 24 hours post procedure, in 24 of 56 participants, finding no significant difference in the interval or length of menstruation compared with before the embolisation. Kim *et al.*¹⁵ measured follicular-stimulating hormone, estradiol and luteinising hormone at baseline, 6 months and 12 months and reported no statistically significant differences before and after the procedure.

No study explicitly included or excluded women who desired a future pregnancy or specifically mentioned active follow-up of future pregnancies, and so reports of pregnancies are not likely to have been systematically collected. Three studies^{15,63,64} reported six successful pregnancies.

Adverse events of embolisation

Six studies did not report any adverse events in their population, although it is not clear whether this equates to technical success in all cases.^{46,51,52,56,57,61} Of the remaining 938 women, in total there were 10 cases of vein perforation causing extravascular leakage of contrast media during the insertion of coils. Transient pain following the embolisation was reported in between 8% and 100% of cases and appeared to occur only in the studies using sclerotherapy, either as the sole embolisation method or in conjunction with coils. One large study of 239 women described early adverse symptoms as a 'post-embolisation syndrome', reporting that 129 (54%) had transient gluteal or lumbar pain, 61 (26%) had general achiness, 30 (12%) had transient fever (≥ 38 °C) and 21 (9%) had mechanical superficial phlebitis at the point of venous access in the arm.⁵⁵

Coil migration after placement was reported in 11 cases; displacement was to the lung in eight cases and the renal vein in two cases, and there was one report of coil protrusion into the femoral vein. In all cases, the coil was retrieved using a catheterised snare, without any lasting harm to the patient.

Individual patient data meta-analysis to explore predictors of effectiveness

One of our stated objectives in this project was to collect IPD from available studies involving embolisation/sclerotherapy in order to identify factors associated with successful outcome, and to perform IPD meta-analysis if possible.

The collection of patient-level data has numerous advantages, including the ability to conduct improved data verification and perform a more comprehensive analysis, including subgroup analysis.¹⁰⁵ However, given the issues outlined earlier in this chapter, we made the decision not to undertake the completion of this objective. These issues included the general low quality of the studies (only one RCT with description of other case series indicating a less than comprehensive design); high variation in interventions and techniques; high variation in the use of outcomes and assessment times; and great inconsistency in the reported characteristics of study participants. IPD meta-analysis is highly resource intensive and we needed to consider the potential cost–benefit of any such undertaking. Our conclusion was that it would be almost impossible to be able to collect and merge enough comparable, high-quality data to make any sophisticated analysis worthwhile.

Discussion

Summary of review findings

This systematic review of embolisation for PVI found no high-quality studies, and so all estimates of effectiveness are derived from presumed prospective case series reporting on 1308 women, the majority of whom were of reproductive age and parous. Approximately one-third of cases clearly had bilateral embolisation, with metal coil placement being the dominant technique.

Early substantial relief from pain symptoms was observed in approximately 75% of 162 patients in six case series, which generally increased over time and was sustained. Where pain was measured on a visual analogue scale, statistically significant reductions following treatment were observed in all studies. Reintervention rates were generally low. Where measured, embolisation reduced the diameter of dilated veins to a significant degree, with minimal residual reflux.

There were few data on menstruation, ovarian reserve or fertility, but no concerns were noted. Transient pain was a common occurrence following foam embolisation, while there was a < 2% risk of coil migration.

Strengths and limitations of the review

The review followed a registered protocol and focused on a clear question for the assessment of effectiveness. A comprehensive search strategy was constructed and used to screen the widest range of bibliographic sources, with selection undertaken by two reviewers. All outcomes identified a priori were reported on, to the extent that data were available. The embolic techniques employed were generally well described, and follow-up data were available for the majority of participants.

The most significant limitation, which prevents firm conclusions being drawn from the data and recommendations being made, is the quality of the studies identified. There is only one RCT of embolisation in the literature, with hysterectomy as a comparison, which was in itself not free of potential biases. Other randomised trials may have been attempted and not published, introducing publication bias, but unless these were of higher quality than that of the study of Chung and Huh,³¹ they would have had little impact on our conclusions. The majority of the studies were relatively small case series, with the inherent high risk of bias, no comparative group and frequently ill-defined inclusion criteria. We attempted

to restrict the studies included to those where participants were prospectively enrolled, to reduce selection bias, but in some studies it was impossible to be completely certain from the methodology that included participants were not retrospectively identified from medical records.

The effect of embolisation on pain was generally described either in terms of symptomatic improvement or as pain scores, reducing the amount of information available for either outcome. We performed a meta-analysis to get a pooled estimate of improvement rates, but may be criticised for doing so using such low-quality data. Few studies sought pain data on individual pain symptoms, such as dyspareunia or pain on standing, preventing reflection on whether or not embolisation reduces specific symptoms thought to be particularly indicative of pelvic vein congestion. The majority of studies gave a description of adverse events, but the long-term impact in fertility was barely considered.

Given the general low quality of studies and extreme variability of patient-reported outcomes, assessment points and participating characteristics in this systematic review, we declined to attempt to collect IPD from the included studies in an attempt to improve the analysis. We may be criticised for this omission, as it is possible that the review would have been enhanced from capture of patient-level data, but we believed that the cost–benefit of such an undertaking would have been too great for this to be worthwhile.

Interpretation

The pooled estimate of moderate to complete symptomatic improvement following embolisation is consistent with a previous review, as are the rates of coil migration, although this too draws on low-quality case series.²⁸ Technical success is high, although dependent on pelvic anatomy, and this technique has been widely adopted around the world, as evidenced by the distribution of studies. Few studies addressed the secondary outcomes of the impact of embolisation on menstruation and fertility; these aspects seem not to be discussed in the literature, which is surprising considering that the target population for pelvic vein embolisation is women of reproductive age. This contrasts starkly with uterine artery embolisation for the uterine fibroids, about which there is considerable debate regarding the impact on ovarian function and pregnancy rates.^{28,106,107} This may simply be because uterine artery embolisation has the potential to disrupt blood flow to, rather than away from, the reproductive organs, but further data are required to reassure women considering the procedure.

Although the data appear supportive, the quality of evidence is poor. Under the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria, the methodological quality is very low and there is no direct comparative evidence against no embolisation.¹⁰⁸ Some reflection on the only RCT is warranted. The study population was thoroughly evaluated to exclude those whose pain could be attributable to organic pathology or who responded to medroxyprogesterone treatment, and who did not wish to retain their uterus and ovaries. The 118 patients were randomised to either embolisation or hysterectomy with bilateral oophorectomy, plus hormone replacement therapy, or hysterectomy with unilateral oophorectomy, on the predominantly congested side. Patients rated their pain on visual analogue scales at 3-monthly intervals after their procedure, and were also stratified according to their stress scores over a recall period of 12 months prior to randomisation.¹⁰³ The study reported that the embolisation group and hysterectomy with bilateral oophorectomy group had statistically significant improvement in pain scores, whereas those with only unilateral oophorectomy did not, but these assertions could not be replicated. Furthermore, the method of randomisation was unclear and there were substantial post-randomisation exclusions, which undermine the credibility of the trial results.

We were unable to investigate the heterogeneity of results across the studies other than for the outcome of moderate to complete symptomatic improvement, reported in six studies, where moderate heterogeneity was identified.^{48,50,53,57,58,63} This could arise from a variety of sources, such as from the embolisation technique, the way in which the question of improvement was presented and categorised or from the population included in the study. We included studies only that intended to report on pain or symptom improvement and yet were able to directly compare outcomes in either the short or medium term in only a minority of studies, which is a concern. We cannot be sure that some studies did collect data on these outcomes, but did not report the outcomes if they failed to show statistical significance or consistent results.

The precision of the estimates for this outcome is moderate owing to the relatively small number of studies and participants per study, with a CI of $\pm 10\%$ around the pooled rate of substantial symptomatic improvement of 75% in the short term. In one of the largest series, 50% of participants had total relief and a further 37% had partial relief at 6 months,⁵⁵ which was consistent with other studies reporting in the 6- to 12-month time frame.^{54,62} This would probably encompass a range of response rates that would be acceptable to women, given the low incidence of adverse events. However, we cannot be certain that publication bias does not exist and that this result is not an overestimation of the true effect, with less incentive for unremarkable results to be reported and commercial pressures not to report poor outcomes. Randomised trials are now almost routinely pre-registered in open-access databases, allowing an assessment of the degree to which there are unreported data, but no such mechanism exists for case series.

If we can accept that embolisation provides pain relief, despite the limitations of the literature, the next questions are whether or not particular presenting characteristics can predict a successful outcome, and what the optimal technique is. A retrospective case series of 41 women assess the relationship between technique (bilateral or unilateral), parity and location of varices (thigh or labial compared with pelvic) and clinical outcome. There was no statistically significant predictor of a successful outcome among these variables, although a trend towards a higher rate of success in grand multiparous women was noted. No association between these variables and treatment failure was observed, but in both circumstances it may just be that there are too few patients for a small association to be observed.⁹⁸

Occlusion of pelvic veins is achieved by means of metal coils, a sclerosant or a combination of the two, according to the radiologist's preference, with no apparent trend for any technique emerging. Stratification of the meta-analysis of symptomatic improvement by coil or sclerosant is limited by the number of data, but seems to suggest that the overall rate of substantial improvement is reflective of the studies using sclerosant at about 75%, whereas the two studies using solely coils had higher rates, at 89% and 100%, respectively.^{57,58} No obvious differences between methods on the reduction in pain scores were seen. In the absence of randomised comparisons, there are no data to indicate superiority of any embolic agent. It may indeed be that the presentation of the varices and anatomy of the veins are the key determinants of successful elimination of reflux, with perhaps both methods being required for the most dilated veins.

Complications of embolisation appear to be limited to short-term pain and fever in a reasonable proportion of sclerosant cases, or an uncommon incidence of coil migration. Coil placement is a relatively straightforward procedure but may be subject to recanalisation or development of collaterals, as has been observed in male varicocele.¹⁰⁹ Some radiologists prefer liquid sclerosant, which can reflux into any collateral veins, owing to its localised effect, the perception that a more extensive embolus is produced, and also the cost compared with metal coils.⁹⁸

Further questions remain regarding the embolisation technique. Should only veins observed to be refluxing be targeted or should bilateral embolisation be the default approach? Should only the OV be embolised, or should the IIV be treated too, and, if so, should this be in the same procedure. The data in our selected studies do not help us to address these controversies. The early experience was mainly of selective embolisation of the left OV,^{57,63} with bilateral procedures becoming more frequent over time. It is not possible to consistently determine from study reports just how many of the later cases of unilateral embolisation were intended or were as a result of difficult access to the right OV. One larger series employed a deliberate strategy of initial OV embolisation followed by repeat venography of the IIV and embolisation where indicated, with 85% having this second embolisation.¹⁵ Pain relief and symptomatic improvement, though, are subjective experiences, and will not be perceived and reported according to the location of the reflux, meaning that it is unlikely any relationship between laterality and improvement would be seen.

Chapter 7 Survey of current practice and prior beliefs of effectiveness of embolisation and other treatments

Introduction

Surveys, in health-care research, are either a method of collecting quantitative information about current practice or serve as opinion polls, assessing the degree of enthusiasm for a research question. Less frequently, the level of awareness of symptoms, diagnosis and treatments available is gauged in the target population. By providing an opportunity for free-text answers, qualitative themes may also be elicited.

Any survey is made up of a number of component parts – the sample, a method of data collection (e.g. a questionnaire), and the individual questions that are asked in the survey – each of which can introduce bias. The purpose of a survey will dictate its focus and whether it is looking to identify preferences, opinions, behaviours or factual information. As surveys are usually based on a sample of the population of interest, the generalisability of the data is dependent on the sample being a fair representation of the target population of interest. Unfortunately, response rates to surveys are notoriously low, raising concerns about non-response bias or the likelihood that non-responding consultees will be systematically different from the population under study. In an age of personal data security concerns, it is often difficult to determine if responders and non-responders are comparable even for basic demographic details.

Web-based surveys, which can be easily e-mailed to large numbers of people, provide a convenient way of distributing and completing surveys. However, one can never be completely certain of the total number of people who actually received the request, or whether or not the intended recipient completed the questionnaire. Modern survey software websites provide tools for creating logical surveys, tracking responses and blocking hackers, and are a frequently used method for creating quality surveys.

In the context of PCS, there are a number of aspects in which the opinion and practice of the relevant professional communities can complement literature-based research. The definition of PCS has been shown in *Chapter 3* to be inconsistent, with the relevant importance of presenting features potentially varying between different specialities. Embolisation, where incompetent pelvic veins are occluded, is a common treatment offered by radiologists, and our review of the evidence in *Chapter 6* suggests that around 80% of patients reported 'good' improvement in their pain symptoms following the procedure. However, there are no data on the number of procedures being performed for this indication in the UK, as hospital episode data are not available at the level of indication, or on the subjective opinion of interventional radiologists as to the effectiveness of embolisation.

If health professionals do not have clear and evidence-based standards for diagnosis and treatment of CPP, it is not surprising that patients will have little awareness and understanding of the syndrome. Women with CPP who have had a 'negative' laparoscopy may not know that some symptoms, such as a dull ache after prolonged periods of standing, are considered by some as typical symptoms of PCS, and hence they will not seek further investigation.

Objectives

To capture all of these aspects, we conducted three surveys, each with slightly different aims. The first was targeted at pelvic pain specialists, with a broad range of questions designed to understand diagnostic criteria and treatment pathways. The second targeted consultant members of the British Society of Interventional Radiology and sought to capture data on the extent, indication and practice of embolisation, and also to elicit opinions about the effectiveness of the procedure. The final survey was sent to the members of a patient support group in order to explore the extent of patient awareness of PCS. The second and third surveys attempted to gauge the level of interest in further research in this area.

Methods

Populations

The first survey took place in May 2013, during the 1st World Congress of Abdominal and Pelvic Pain conference in Amsterdam, the Netherlands. This was the inaugural congress of the Abdominal and Pelvic Pain Specialist Interest Group of the IASP and was attended by over 500 abdominal and pelvic pain professionals from 10 disciplines and no fewer than 46 countries. The congress organisers could not provide the e-mails of the attendees, as consent had not been given for contact by third parties, or provide conference bags to attendees. Therefore, to promote the survey, A5-sized invitation postcards were handed to people as they were exiting a plenary session and were also strategically placed in the congress centre. The card gave a brief statement about the purpose of the survey, a weblink to the online survey and a QR code (quick response code) to facilitate completion of the survey on a smartphone. It is estimated that approximately 300 postcards were handed out or taken.

The second survey was sent to consultant members of the British Society of Interventional Radiology in October 2014 by e-mail, from the society secretariat, as again their membership had not given consent for third party contact. This contained a weblink to an online questionnaire and stated that the survey was part of a National Institute for Health Research research project. The e-mail was sent to approximately 600 e-mail accounts, although how many were received and opened is unknown.

The third survey was sent to female members of the Pelvic Pain Support Network (PPSN), who were not health professionals and had, at some point, asked to join the mailing list of this group. The weblink to the survey was distributed in October 2014 from the group's e-mail address to approximately 800 members. The invitation and survey title did not include the phrase 'pelvic congestion syndrome', but did state that the intention was to explore understanding of a rare cause of CPP.

Questionnaire framework

Each questionnaire was tailored to the aim and the target population, with 15, 11 and 7 questions in total in the three surveys, respectively. The surveys were undertaken through SurveyMonkey™ (www.surveymonkey.com; Palo Alto, CA, USA), an online survey development website that enables users to create and publish professional questionnaires online. The package used enables in-built logic, whereby the answers to a question can direct the respondent to particular subsequent questions. It allows respondents to reverse through the questionnaire to edit responses, while making some answers mandatory.

Questionnaire items

The individual questions for the three surveys are shown in *Tables 14–16*, respectively. Questions were closed, with single answers, multiple answers or ordinal frequency responses (usually, sometimes and never). Two radiologists piloted the second survey, while the chairperson of the PPSN reviewed the third. Not all questions in the survey were mandatory; those that are have a footnote marker in *Tables 14–16*. Free-text fields were provided for responses not falling within our categories and for general comments.

TABLE 14 Survey 1: pain specialists attending the World Congress of Abdominal and Pelvic Pain

Question number	Question text	Response options		
1 ^a	Please indicate your specialty	Gynaecologist/ gynaecological surgeon	General surgeon	Family physician
		Nurse/nurse specialist	Interventional radiologist	Other (please specify)
2	In which country do you work?			
3 ^a	To you, what are the important observations for a diagnosis of PCS?	Dull pain exacerbated by standing up	Refluxing and incompetent OV's	Visible vulval or groin varices
		Dyspareunia	Refluxing and incompetent pelvic veins	Ovarian and renal vein compression by superior mesenteric artery
		Dilated OV's	Dilated pelvic veins	Iliac vein compression against the spine/pelvis
		Tortuous/twisted venous plexuses		
4	Which imaging methods do you use to diagnose PCS?	Usually	Sometimes	Never
	TAUS alone			
	TAUS with Doppler			
	TVUS alone			
	TVUS with Doppler			
	MRI			
	MR venogram			
	CT			
	Laparoscopy			
	Fluoroscopic venogram			
	Transfundal venogram			
	Other (specify)			
5	Approximately how many diagnoses of PCS do you make annually?			
6	Any comments on the number of cases of PCS you see?			
7 ^a	Do you treat PCS medically?	Yes, always	Yes, sometimes	No, never
		Go to Q8	Go to Q8	Skip to Q9

continued

TABLE 14 Survey 1: pain specialists attending the World Congress of Abdominal and Pelvic Pain (*continued*)

Question number	Question text	Response options		
8 ^a	If yes, which treatments do you offer? GnRH agonists alone GnRH agonists with oestrogen add-back Progestins/progestogens Dihydroergotamine Non-steroidal anti-inflammatory drugs Combined oral contraceptive pill Antidepressants Other (please specify)	Usually	Sometimes	Never
9 ^a	Do you treat PCS surgically?	Yes	I refer to a surgeon Skip to Q11	No, never Skip to Q12
10	Which surgical procedures do you perform? Laparoscopic OV ligation Hysterectomy Hysterectomy with bilateral salpingo-oophorectomy Other (please specify)	Usually	Sometimes	Never
11	If you refer to a surgeon, what are your criteria for referral?			
12 ^a	Do you treat PCS radiologically?	Yes Go to Q13	I refer to a radiologist Skip to Q14	No, never Skip to Q15
13	Which radiological procedures do you perform? Embolisation with coil Embolisation with foam Embolisation with beads Other (please specify)	Usually	Sometimes	Never
14	If you refer to an interventional radiologist, what are your criteria for referral?			
15 ^a	Do you treat PCS with other therapies?	Yes Go to Q16	I refer to a therapist Skip to end	No, never Skip to end

TABLE 14 Survey 1: pain specialists attending the World Congress of Abdominal and Pelvic Pain (*continued*)

Question number	Question text	Response options		
16 ^a	Which other therapies do you offer or refer? Physical therapy Psychological therapy Acupuncture Other (please specify)	Usually	Sometimes	Never
a Mandatory questions.				

TABLE 15 Survey 2: consultant members of the British Society of Interventional Radiology

Question number	Question text	Response options		
1 ^a	Do you currently perform pelvic vein embolisation in women with CPP and pelvic vein insufficiency?	Yes Go to Q2	No Skip to the end	Any comments
2 ^a	To you, what are the important observations for consideration of pelvic pain embolisation?	Dull pain exacerbated by standing up Dyspareunia Dilated OVs	Dilated IIVs Tortuous/twisted venous plexuses in the pelvis Refluxing and incompetent OVs	Refluxing and incompetent pelvic veins Visible vulval or groin varices Ovarian and renal vein compression by superior mesenteric artery Iliac vein compression against the spine/pelvis
3	Which imaging methods do you use to identify pelvic vein reflux before discussing embolisation with the patient? TAUS alone TAUS with Doppler TVUS alone TVUS with Doppler MRI MR venogram CT Laparoscopy Fluoroscopic venogram Transfundal venogram Other (specify) If other, please specify	Usually	Sometimes	Never

continued

TABLE 15 Survey 2: consultant members of the British Society of Interventional Radiology (*continued*)

Question number	Question text	Response options		
4 ^a	Approximately how many pelvic vein embolisations have you performed in your career?			
5	Which interventional radiological procedures do you perform? Embolisation with coils Embolisation with a sclerosant Other (please specify)	Usually	Sometimes	Never
6	What is your preferred type of coil?			
7	What is your preferred type of sclerosant?	Alcohol-based sclerosant Glue/cyanoacrylates	Sodium tetradecyl sulphate Liquid embolic agents, e.g. Onyx	Other (please specify)
8	Would you offer embolisation to women who desired a pregnancy in the future?	Yes	No	
9	Have you ever observed any serious adverse events following pelvic vein embolisation?	Yes	No	If yes, please describe type and number of times observed
10	We want to ask you about your beliefs regarding the effectiveness of embolisation	Complete or significant reduction in pelvic pain	Moderate reduction in pelvic pain	Very small reduction in pelvic pain No reduction or worsening of pelvic pain
11 ^a	Do you consider there is sufficient evidence to justify offering pelvic vein embolisation to all women with CPP and pelvic vein insufficiency?	Yes, I think there is sufficient evidence	No, I think there is a need for evidence from RCTs	

a Mandatory questions.

TABLE 16 Survey 3: to women on the mailing list of the PPSN

Question number	Question text	Response options		
1 ^a	Have you heard of PCS as a cause of CPP in women?	Yes Go to Q2	No Skip to the end	
2 ^a	Have you been told PCS is, or might be, the cause of your pelvic pain?	Yes, I have been diagnosed with PCS as the cause of my pelvic pain No, I have (or did once have) pelvic pain but have not been diagnosed with PCS	Not quite, my doctors have suggested I might have PCS but are not certain it is the cause of my pain No, I do not have pelvic pain	
3	What are the symptoms of PCS?	I do not know Pain during periods Pain from contractions of the vagina during sex Varicose veins on the inner thigh or buttock crease Increased urgency to go to the toilet to defecate (poo)	Dull pain made worse by standing for a long time Pain between periods Varicose veins in the back of the leg Haemorrhoids (piles) Other symptoms (please specify)	Dull pain made worse by lying down for a long time Pain inside during penetrative sex Varicose veins on the vulva Increased urgency to go to the toilet to urinate
4	What sorts of women are more likely to have PCS?	I do not know Women who have passed the menopause Women who have given birth vaginally Women who are very thin or underweight	Women aged under 25 years Women who have not had a baby Women who have had at least one caesarean delivery Women who are overweight or obese	Women aged between 25 and 50 years Women who have had three or more children Women of a particular ethnic group Other groups of women (please specify)
5	Do you know what the best methods are to diagnose PCS?	I do not know Ultrasound on the lower abdomen Laparoscopy – camera investigation through the belly wall MRI or CT scan of pelvic area	Asking about symptoms Ultrasound in the vagina Endoscopy – camera investigation via the bowel Venography – injecting dye into veins and an X-ray	Examination of pelvic area Hysteroscopy – camera investigation via the vagina X-ray of bones in pelvic area

continued

TABLE 16 Survey 3: to women on the mailing list of the PPSN (*continued*)

Question number	Question text	Response options		
6	Do you know what treatments might be offered to women with PCS?	I do not know	Contraceptive pill	Progesterone-only pill (mini-pill, Cerazette®)
		Contraceptive coil, implant or injection	GnRH agonists (Zolodex®, Lupron)	Surgical clipping of OVs
		Blocking of veins in pelvis by glue or metal coils	Blocking of leg veins by glue or metal coils	Hysterectomy only (removal of the womb)
		Hysterectomy with removal of ovaries	Other treatment methods (please specify)	
7	Do you think there should be more research on vein blocking for PCS?	No, if thousands of women have had veins blocked and improved, then no more research is needed	Yes, it sounds like there is still some uncertainty about vein blocking	Other thoughts about more research
		I do not know		

a Mandatory questions.

In the survey to the support group members, the final question, regarding the need for further research, was contextualised with the following preamble:

Embolisation is the first choice of treatment for PCS. There is a wealth of data from women who have had this procedure, of which 80% have reported an improvement in pain following embolisation. Even though there is this overwhelming evidence, NICE [National Institute for Health and Care Excellence] and other professional bodies representing gynaecologists and radiologists do not recommend the use of pelvic vein embolisation. This is because they do not feel the evidence base on embolisation, compared to other or no treatment, is strong enough.

Data synthesis

SurveyMonkey provides analytical tools in the package which allow the option to present data as histograms or export to a Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) spreadsheet for further manipulation. Results are presented here as percentages and frequencies, with histograms for some questions.

Results

Survey 1

A total of 18 responses were received, giving an estimated response rate of 6%. The majority of respondents were gynaecologists or gynaecological surgeons (44%, 8/18), followed by pain specialists (28%). Other specialists completing the survey included urologists/urology specialists (17%) and sexual health specialists (11%). Respondents were mainly from the UK or the rest of Europe (83%, 15/18); the remainder were individuals from Australia and Philippines. One respondent failed to disclose their location.

Diagnosis of pelvic congestion syndrome

When those surveyed were asked what the most important observations were for a diagnosis of PCS, the following four symptoms were the most popular answers (respondents were asked to select as many as they believed applied): dull pain exacerbated by standing up (33%, 6/18), dyspareunia (22%, 4/18), dilated OVs (28%, 5/18) and dilated pelvic veins (39%, 7/18). Other selected observations included tortuous/twisted venous plexuses (11%, 2/18), refluxing and incompetent OVs (6%, 1/18) and refluxing and incompetent pelvic veins (17%, 3/18). Irrelevant observations, not selected by any respondent, were visible vulval or groin

varices, ovarian and renal vein compression by superior mesenteric artery and iliac vein compression against the spine or pelvis. One respondent reported, as free text, a patient having difficulties during sex due to too much lubrication.

There were two dissident respondents. One stated that had not diagnosed a single case of PCS in 10 years in the pelvic pain field and had only very rarely seen dilated veins at laparoscopy, and they believed these to be coincidental. Another was not convinced that PCS, as a condition, even existed, believing that symptoms were due to endometriosis or adenomyosis not visible at laparoscopy.

In terms of the imaging methods used to diagnose PCS, respondents were asked to rate their usage of each test, as illustrated in *Figure 5*. Eight respondents skipped the question completely (with one describing it as not applicable) and, as responses were not mandatory, the number of responses per test varied from three to eight.

Transvaginal ultrasound with Doppler and laparoscopy were the most frequently used techniques. Four people usually used laparoscopy and two used it sometimes; this was the same for TVUS with Doppler, with four using TVUS alone (three usually and one occasionally). One or two individuals did not use these three techniques. Three people used TAUS.

One respondent said that he or she frequently used MRI, and another used this occasionally, while only one respondent used MR venography, and then only occasionally. Only one respondent used CT, and this was frequent. Fluoroscopic percutaneous or transfundal venograms were not used by any respondents.

Among those who specifically reported avoided using an imaging method, four never used TAUS, MR venograms and CT, while one did not employ laparoscopy.

Prevalence of pelvic congestion syndrome

When those surveyed were asked approximately how many diagnoses of PCS they made per year, the 10 answers given ranged from none in three cases to 20–25 by one respondent, with the remaining six respondents seeing 1–5 cases.

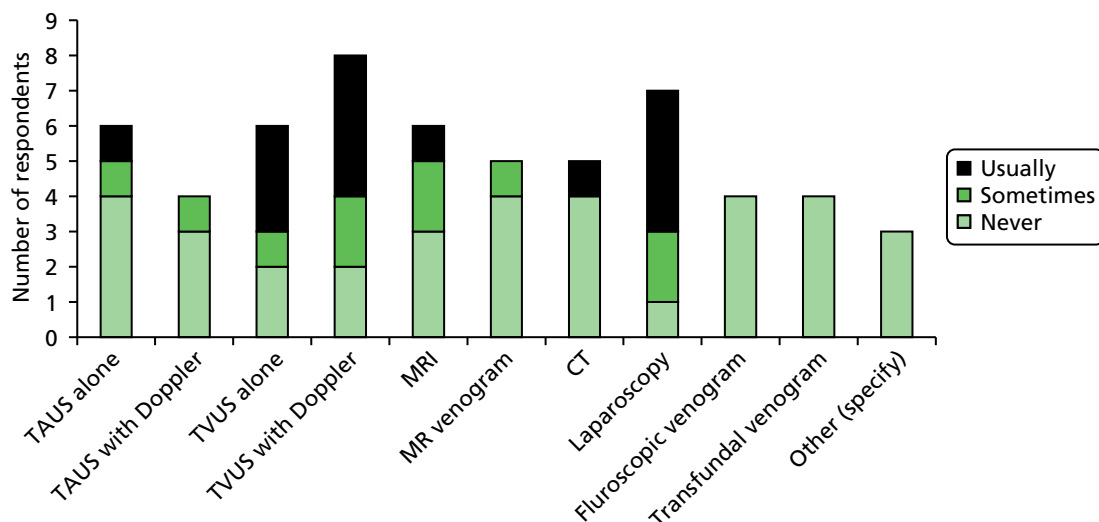


FIGURE 5 Survey 1, question 4: which imaging methods do you use to diagnose PCS?

Several comments were made alongside answers to this question. The same respondent who questioned the existence of PCS in the previous question retorted that they tended to look for another, more 'justifiable' cause for the pain in their use of tests. One respondent wondered if pelvic floor trigger points could produce the same pain symptoms as PCS and hypothesised that although menorrhagia, increased discharge and pelvic ache may suggest a diagnosis of PCS, this does not necessarily correlate well with the finding of dilated veins. A further noteworthy point made by one respondent was that he or she felt that PCS was underdiagnosed, stating '... there are more'. Another respondent, who reported seeing an average of five cases a year, went further and said that, at present, he or she was struggling to diagnose PCS and that more research would be welcomed to improve understanding of the condition. One further respondent said that he or she was now taking a diagnosis of PCS into consideration for women with unexplained pelvic pain.

Medical treatment of pelvic congestion syndrome

Seven respondents did not answer this question. Of the 11 who did answer, two (18%) always treated PCS medically, two (18%) sometimes treated PCS medically and seven (64%) never did this. Among the four respondents who indicated that they treated PCS medically, three usually chose the combined oral contraceptive pill, non-steroidal anti-inflammatory drugs (NSAIDs) and GnRH agonists with oestrogen add-back to do this, while three sometimes offered antidepressants and two offered either progestogens or NSAIDs. One respondent stated that they never used GnRH agonists with or without oestrogen or dihydroergotamine. An additional comment provided by one respondent explained that they would only see a patient with this diagnosis once other interventions had failed, and would at that stage perhaps offer the patient antidepressants and NSAIDs.

Surgical treatment of pelvic congestion syndrome

No respondents said that they would treat PCS surgically themselves, although three – one gynaecologist, one urologist and one describing him- or herself as a primary care sexologist – would refer the case to a surgeon, but they did not state their referral criteria. Five respondents, all gynaecologists, stated that they would never treat PCS surgically. As no respondents said that they would treat PCS surgically, the following question regarding surgical procedures (laparoscopic OV ligation, hysterectomy, hysterectomy with bilateral salpingo-oophorectomy and other) was void. Seven respondents did not answer this question.

Radiological treatment of pelvic congestion syndrome

When asked if PCS would be treated radiologically, none of the 11 responded positively, as there were no radiologists in the sample. Two of respondents said they would refer the case to a radiologist; however, many more (9/11, 82%) stated that they would not treat PCS radiologically. As before, this made the following question about radiological procedures void. One of two respondents who said that they would refer patients to an interventional radiologist stated that positive findings on MRI, and probably laparoscopy, would be among the criteria they would use for referral.

Other therapies for pelvic congestion syndrome

When respondents were asked if they would use any other therapies to treat PCS, seven (64%) said no, three (27%) said that they would and one said that he or she would refer the patient to a therapist. Among the four proponents of other therapies, physical therapy was the usual (two respondents) or frequent (two respondents) choice, while psychological therapy was the usual choice of one person and the occasional choice of two others. Two of the respondents would consider acupuncture. Two further suggestions were sexual therapy (suggested by the sexologist) and neuromodulators, although no further details were given. Seven respondents did not answer this question.

Survey 2

Survey 2 was initiated by 63 respondents, giving an estimated response rate of 10%. The initial screening question asked whether or not radiologists were currently performing pelvic vein embolisation in women with CPP and PVI; 47 out of 63 (75%) respondents answered positively. The remaining 18 were diverted to the final question.

Twelve respondents made additional comments to accompany this question. Three did not currently undertake embolism, although one had done this previously and another indicated that it was done within his or her department; the third stated that he or she 'could not get my clinician colleagues to believe there is such a thing' as PCS. Of those respondents who did currently undertake embolisation, at least five reinforced the infrequency of this procedure, although one stated that the number of women he or she saw had been slowly increasing over time. Three radiologists related their embolisation practice to the treatment of varicose veins. One used embolisation for varicose veins in the leg, which originated in the pelvis, and noted that although most of these patients had PCS, they were not referred specifically for that reason. Another commenter echoed this sentiment, saying that for them, pelvic vein embolisation was usually for leg varicose veins and/or vulval varices, and rarely for PCS alone. A third respondent stated that his or her largest group of patients had PVI associated with lower-limb varicosities. A further respondent highlighted the need for a multidisciplinary team approach, which would include a vascular surgeon (with an interest in PCS), a vascular ultrasound specialist and a gynaecologist.

Diagnosis of pelvic congestion syndrome

The 45 respondents who undertook embolisations were asked to subjectively choose all of the symptoms and observations that they felt were important in order for pelvic vein embolisation to be considered (Figure 6).

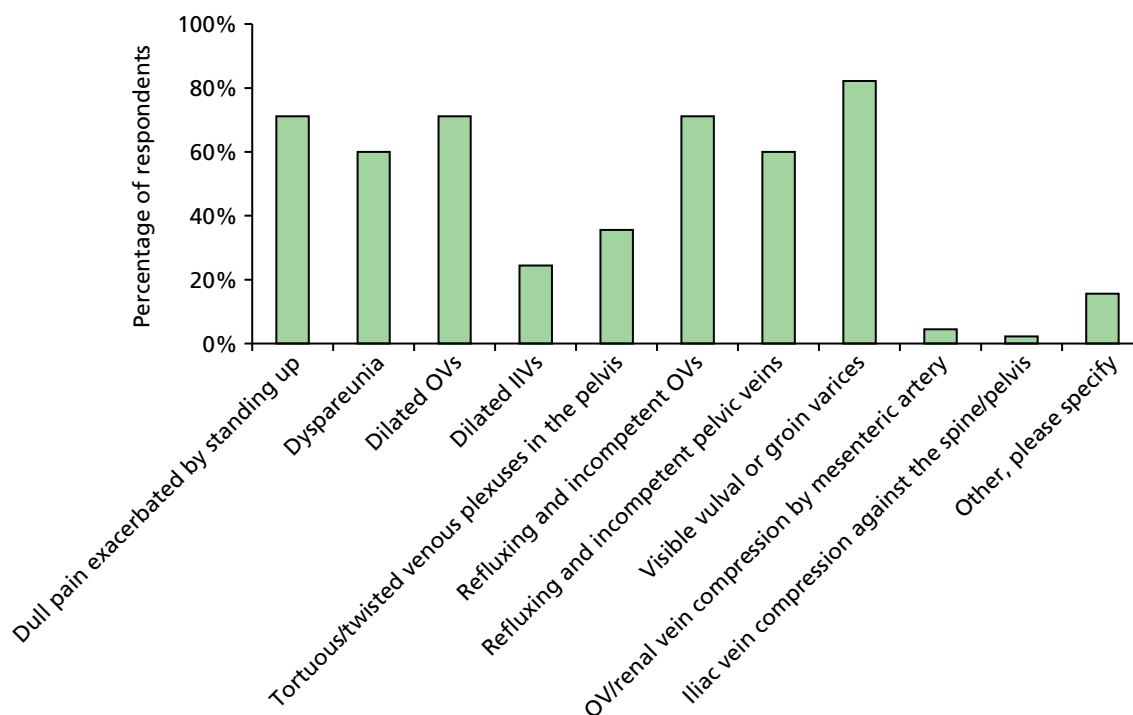


FIGURE 6 Survey 2, question 2: to you, what are the important observations for consideration of pelvic vein embolisation?

With regard to patient-reported symptoms, 32 out of 45 respondents (71%) regarded dull pain exacerbated by standing up as an important observation to necessitate embolisation, while 27 respondents (60%) considered dyspareunia important. Dilatation of the OV was a criterion for 32 (71%), but only one-quarter thought the same for dilated IIVs. Only 16 (36%) considered tortuous pelvic veins important. With regard to refluxing and incompetent veins, around two-thirds rated the OV and other pelvic veins as crucial, but this was surpassed by the 37 (82%) who considered visible vulval or groin varices important. The radiological condition of Nutcracker syndrome was generally discounted. The median number of signs and symptoms considered as indications was five.

Other important indications suggested by respondents in open responses included irritable bowel syndrome, bladder instability, labial varicosities, negative laparoscopy findings for other causes of pain and non-cyclical pelvic pain. The relationship with varicose veins and communicating pelvic veins was reiterated. Another respondent related the criteria they used to those they applied to treating a varicocele in men, during which treatment they embolised any gonadal vein that was distended and could be creating venous pressure into the pelvis.

In terms of the imaging methods used to diagnose PCS, respondents were asked to rate their usage of each test, as illustrated in *Figure 7*. As a response for each test was not mandatory, the number of responses per test varied from 8 to 36 of 45 respondents.

Magnetic resonance venography was the most frequently used technique, with 17 of 36 (47%) respondents usually employing it, 16 using it often and only 3 never using it. Traditional venography was the most consistently used technique, with 22 out of 34 respondents stating that they used this method. Ultrasound with Doppler was preferred to simple ultrasound, with transvaginal and transabdominal scans being equally popular and comparable with CT. Transfundal venogram appeared to be an obsolete technique.

The responses to the open-ended questions suggested there could be a staged approach to diagnosis, reflecting the clinical situation in which venography immediately precedes embolisation. One respondent indicated that he or she would choose TVUS with Doppler as their first-line imaging test; another aimed to perform Doppler ultrasound of the leg veins, which, if it showed that they originated from the pelvis, would prompt a fluoroscopic venogram, with consent from the patient to perform embolisation if appropriate. Another respondent held conflicting views, stating that he or she found non-invasive imaging methods unreliable and would instead proceed straight to conventional venography.

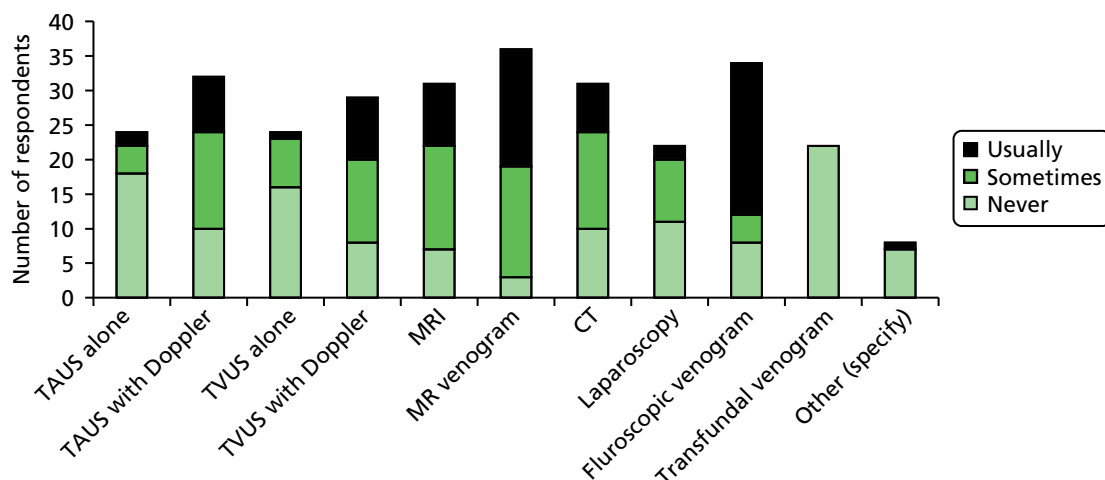


FIGURE 7 Survey 2, question 3: which imaging methods do you use to identify pelvic vein reflux before discussing embolisation with the patient?

Number of procedures performed

Among the 45 radiologists who undertook pelvic vein embolisations, the number of procedures performed over their careers ranged from 1 to 1100. The majority had performed fewer than 20, but 4% had performed over 500 (Figure 8).

Embolisation method

Twenty-two respondents did not answer this question. Embolisation with coils was the usual procedure of 40 of the 41 respondents (98%), while only 6 of 34 (18%) usually used sclerosant and a further 12 (35%) used this occasionally. Nearly half stated that they never used sclerosant. One respondent stated that, besides the procedures mentioned above, they used 'plugs'.

When the respondents were asked about their preferred type of coil, soft fibre-coated platinum helical coils (Nestor™, Cook Medical, Bloomington, IN, USA) were a popular choice, with 14 out of 40 (35%) indicating that they used these, followed by platinum spiral coils (Spirale™, Pyramed, Robina, QLD, Australia), used by 30% of respondents; three used a combination of both coils. Others did not name brands of coil but just described ideal characteristics, such as platinum fibred, long, pushable, 'whatever will fit' or as indicated by diameter and location.

The choices given for preferred type of sclerosant were constrained to four types referred to in the literature. Of the 22 who answered this question with a preference, the overwhelmingly most popular choice was sodium tetradecyl sulphate, preferred by 19 respondents. Glue or cyanoacrylates, liquid embolic agents (Onyx™, Covidien Ltd, Dublin, Ireland) and polidocanol were each preferred by one respondent, while no respondent reported using an alcohol-based sclerosant. Over three-quarters of radiologists said that they would offer embolisation to women who desired a pregnancy in the future (32/41).

Incidence of serious adverse events following pelvic vein embolisation was low, being reported by only 4 of 41 respondents. Ignoring transient post-embolisation symptoms and minor access site injuries, nine cases of coil migration to the lung and one to the renal vein were reported, along with one case of vaginal bleeding.

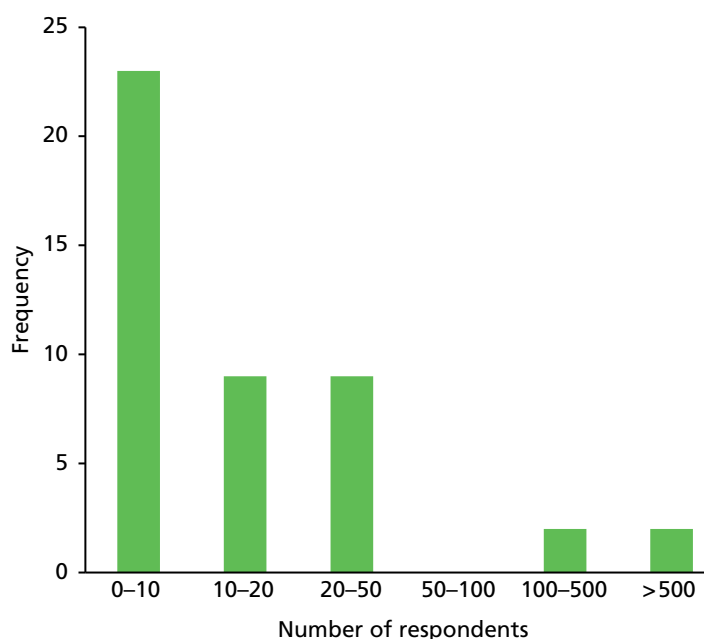


FIGURE 8 Survey 2: distribution of number of procedures performed by interventional radiologists in their career.

Effectiveness of pelvic vein embolisation

This question was asked to estimate the range of radiologists' beliefs about the effectiveness of embolisation. Respondents were asked, if embolisation was performed using ideal technique at the hands of an experienced radiologist, in patients with clearly defined PVI, how they would rank the probability of the following four outcomes, collected from the patient at 6 months, and then compared with pain before the procedure. The four outcomes were complete or significant reduction in pelvic pain, moderate reduction in pelvic pain, very small reduction in pelvic pain and no reduction in or worsening of pelvic pain. Respondents were asked to assign a percentage probability to each outcome, ensuring that the total added up to 100%. Responses are presented as weighted average percentages in *Figure 9*.

Potential for a future randomised trial of embolisation

At present, there are no RCTs comparing embolisation with no treatment or medical treatment. The final question asked respondents if they felt that there was sufficient evidence to justify offering pelvic vein embolisation to all women with CPP and pelvic vein insufficiency. Eight of the 50 who responded (16%) felt that there was sufficient evidence, while the overwhelming majority thought that the evidence base could be strengthened by data from RCTs.

Comments came predominantly from those who believed that there was a need for further research. Dissenting opinions were that embolisation offers a good treatment for at least half of patients and that there are no really effective surgical alternatives for patients with significant symptoms. Such views were qualified, though, with respondents stating that a multidisciplinary clinic with gynaecologists with a special interest in pelvic pain was the appropriate setting in which to offer embolisation.

Open responses from proponents of further research were grouped into themes around diagnosis, any comparator, assessment of effectiveness and overall opinions. Six radiologists highlighted the controversy around PCS per se and the lack of clear diagnostic criteria. One questioned why there was such wide international variation in the number of referrals to interventional radiologists from gynaecologists. The exclusion of other pathological causes and venographical confirmation of reflux was considered essential by two of the 15 radiologists who provided open comments. Another mentioned an audit in their own facility which found that most women with varicose veins had symptoms of PCS, reiterating their response to previous questions in which they stated their belief that PCS was an under-reported phenomenon.

In considering the design of a randomised trial, one respondent questioned whether a sham treatment arm would be acceptable. In terms of outcomes, in addition to a subjective measure of improvement, other outcomes deemed important were a measure of venous pressure and recurrence rates, while identification of predictive variables of success would be useful.

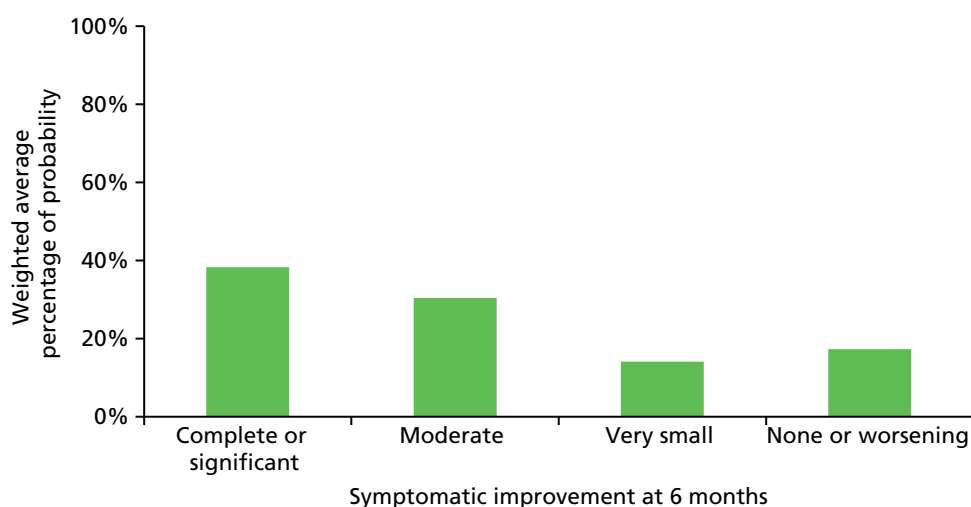


FIGURE 9 Survey 2: distribution of beliefs regarding the effectiveness of embolisation for PCS.

Several respondents reiterated their belief that a RCT was required, noting that, were there sufficient evidence, embolisation would be more widely offered. Some noted that when they counsel patients and attempt to manage their expectations, they emphasise the fact that although the procedure has very few complications, there is little reliable evidence as to its effectiveness.

Survey 3

From the e-mailshot, 69 women commenced the survey, representing a response rate of approximately 8%. We first ascertained how many respondents were familiar with the term 'pelvic congestion syndrome' as a cause of CPP in women. Our results found that fewer than half of the women had knowledge of PCS (32/69, 46%). As the remaining questions were designed to explore women's understanding of PCS, those who were unaware of PCS were diverted to the end of the survey, reassured that PCS was an under-recognised and rare cause of CPP and thanked for their contribution. Of those who were aware of the condition, 3 out of 32 (9%) had received a diagnosis of PCS as the cause of their pelvic pain, with one woman having been told that PCS may be the cause of her pain. Other than one respondent who did not have pain, the remainder either had or at one time had pelvic pain, but they had not been diagnosed with PCS.

Symptoms and patient characteristics of pelvic congestion syndrome

Figure 10 shows the distribution of responses from 30 women, when they were asked which symptoms they thought were indicative of PCS. Six respondents admitted that they did not know, while the remainder selected an average of five symptoms. Symptoms were described in lay terms, which we also use here.

The symptom identified by the most respondents (21/30; 70%) was a dull pain made worse by standing for a long time. The next most frequent symptoms, each reported by 43–46% of women, were pain between periods, pain during periods and pain inside during penetrative sex. The remaining symptoms were selected by between 20% and 27% of respondents.

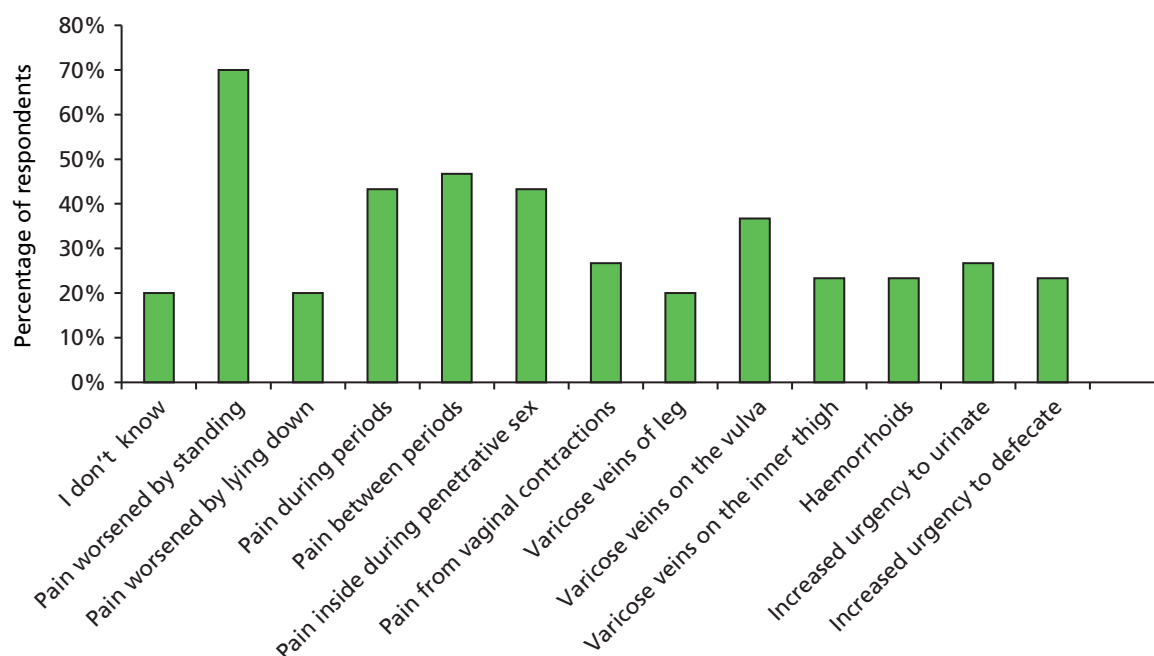


FIGURE 10 Survey 3: symptoms considered indicative of PCS by women with CPP.

To assess their perception of the risk factors, respondents were asked for the characteristics of women who they felt were more likely to have a diagnosis of PCS. Over half of the 30 who responded were unsure. All of the remaining 13 believed that PCS was a condition of women of reproductive capability. One thought that nulliparity was a risk factor and two identified grand multiparity, and while three thought that vaginal delivery was important, none thought that PCS was associated with caesarean delivery. Three also thought being overweight was a risk, but that ethnicity was not. Four qualified their choices by stating that PCS was a condition that any woman could develop.

Diagnosis and treatment of pelvic congestion syndrome

When asked about diagnostic tests for PCS, nine respondents (32% of 28 who answered) did not know. Of the remaining 19, laparoscopy was considered the most frequently cited, by 63%, followed by taking a history of symptoms (11 of 19, 58%), ultrasound (seven believing that transabdominal and five believing that transvaginal scans were required) and then MRI or CT and venography (each 9 of 19, 47%). On average, 3 or 4 tests were selected, and one respondent also mentioned conscious pain mapping.

When asked what treatments respondents thought women with PCS might be offered (aside from painkillers), again around half, 13 out of 28 (46%), did not know. Of the remainder, embolisation was cited by 9 (of 15, 60%), with the combined oral contraceptive pill, GnRH agonists and surgical clipping of OVs being selected five times. The remaining options were selected by three people or fewer.

Potential future research

A total of 28 respondents answered this question; the majority (64%) indicated that they believed more research should be done, with only two disagreeing, although eight (28%) indicated that they did not know. Further thoughts provided by some of the respondents generally expressed a desire for more research on CPP in general. One respondent specifically highlighted a need for research into the role of pudendal and vulval nerve damage. Two of the responding women showed specific insight in calling for a review of current research or for a randomised trial of embolisation against GnRH agonists or no treatment. The final comment provided reiterated the need for women with CPP to be listened to, which would drive the research agenda.

Discussion

Key findings

We undertook three surveys to get a broad perspective of current understanding and management of PCS, eliciting responses from those with a specialist interest in pelvic pain, from interventional radiologists and from women with CPP. Although this work predominantly focuses on the UK, we believe that it represents the only recent and relevant review of management of PCS, beyond the case series discussed in *Chapter 6*.

A few key themes can be drawn out from the surveys:

- There is variation between pain specialists and interventional radiologists in their approach to diagnosis.
- Surgical management does not appear to be favoured.
- The majority of interventional radiologists do not perform many, if any, embolisations for PVI, and although their confidence in the procedure is reasonably high, there is a desire to strengthen the evidence base.
- Even among women with CPP, fewer than half had any knowledge about PCS.
- There remain some dissenting opinions regarding PCS as a cause of CPP.

Strengths and limitations of the surveys

Surveys can be unrepresentative if they collect information from only a limited number of people and if those who do respond are not representative of their constituency. Unfortunately, all three surveys were limited in size, both initially in the number of people connecting to the SurveyMonkey questionnaire and in those who answered affirmatively to the first question of the second and third surveys, which was designed to select those with experience or understanding of PCS. As discussed before, it was not possible to compare any characteristics of responders and non-responders among the British Society of Interventional Radiologists membership, so it is likely that the respondents are those for whom embolisation is more pertinent. The low response rates to all three surveys are of concern, but not unique. A recent web-based survey of the membership of the European Society of Gynaecological Endoscopy, regarding laparoscopic morcellation practice, generated a response rate of around 5% (ESGE Secretariat, 2014, personal communication). There was no monetary incentive for completing the survey; vouchers for credit at online retailers are increasingly used to boost response rates. The second and third surveys were open for response for only 2–3 weeks, with no reminder sent to non-responders, although the SurveyMonkey analytics show that the peak time for responses was within a few days of the e-mailshot, so further reminders would have been likely to give diminishing returns.

Short surveys are more likely to be completed in full. We could see some diminution in the number of respondents in later questions in each survey, possible reflecting question fatigue. For the questions in which frequencies were ranked, in retrospect it would have been beneficial to require a response for each queried test or treatment, so that the relative proportions choosing usually, sometimes or never always totalled the same. We can only infer that those not providing a rating for each test or treatment had never used that test or treatment. The ability to skip past questions was useful in the first survey. We did not know the spectrum of professions who would respond when we designed the survey, so we attempted to cover a broad range of management aspects. The terminology used in the later surveys was improved as a result of feedback from the first survey.

Online surveys are undoubtedly a popular modern method for collecting data and provide advantages such as instant analysis of the data. They are, however, restrictive in the type of questions that can be asked, to some extent. We were not able to elicit respondents' beliefs about the effectiveness of embolisation in a way that would provide a subjective probability for a range of potential effects. Previous methods of numerically representing beliefs have involved respondents being provided with a range of outcomes and a visual analogue scale for each outcome.¹¹⁰ In order to apply this technique in our situation, we would have had to present a list of perhaps 11 options on a spectrum ranging from, at one end, embolisation providing 100% symptomatic improvement, to 80% improvement, to 60% improvement, to no benefit over no treatment, and finally to the other extreme of possible treatment effects, namely embolisation worsening the pain. Respondents would use the visual analogue scale to mark their subjective estimation of the probability of each outcome, on an anchored line from impossible, to increasingly likely, to certain. Previous users of this approach have tended to undertake this exercise while the respondents are present, for example at a meeting; this allows the users to explain the objective of the survey and provide instructions to the respondents on how to complete the visual analogue scale.

However, although marking such a scale on paper is easy, SurveyMonkey does not provide the equivalent of a visual analogue scale. The approach we chose was an adaption of a weighting method,¹¹¹ albeit with four non-numerical categories. We asked radiologists to assign a distribution of probabilities, forcing the responses to sum to 100%. Our primary outcome was symptomatic improvement, which is a subjective outcome itself and so would be variably interpreted by radiologist. Despite this, we can report that about 38% of radiologists believed that embolisation would provide a complete resolution of symptoms or significant improvement, whereas 18% believed embolisation would not provide an improvement in symptoms or would worsen them.

Interpretation

Pain specialists and radiologists both considered dilated pelvic veins as highly indicative symptoms of PCS, although even more radiologists appeared to rank visible vulval varices as a relevant observation and one-third of women were aware of this as a symptom. All three groups considered dull pain from prolonged standing to be important, although this is rarely described in the definitions of PCS reviewed in *Chapter 3*.

Pain specialists and radiologists diverged to a certain extent in their chosen diagnostic methods, which probably reflects their respective positions in the management pathway of women with CPP. The former were more likely to use ultrasound and laparoscopy, procedures that they were likely to be capable of performing and which would also be part of the typical gynaecological investigation of CPP. MR or fluoroscopic venograms were the preferred methods of radiologists, which is unsurprising given that they constitute the definitive method of identification and localisation of PVI and would be undertaken prior to embolisation. Female members of the support group, perhaps influenced by their personal experiences, believed that three or four tests would be required. Although laparoscopy was frequently cited, it is thought by some to underestimate the true prevalence of PVI. It does, however, have its place in eliminating other pathological causes of CPP.

In the limited sample of pain specialists, very few were inclined to offer medical treatments, and there was no clearly preferred treatment. This reflects the fact that women may have already tried various medical treatments to no avail. It has been noted that it can take years for a woman to obtain a diagnosis of endometriosis,⁷ and it is likely that the same issues apply for PCS, given the uncertainty around its definition. No respondents, including the gynaecologists, proposed surgical treatment. This is not entirely unexpected, as hysterectomy is a major operation and perhaps should not be considered while there are non-invasive alternatives available, although ligation of the ovarian arteries may achieve the same effect as embolisation. Hysterectomy with oophorectomy has been used historically and was the comparator in the only randomised trial of embolisation.³¹ This observation also vindicates our decision to exclude pelvic ligation from our review in *Chapter 6*. Only a minority of pain specialists considered acupuncture and physical and psychological therapies, which was perhaps unsurprising given that for CPP in general there is little evidence for any non-surgical or non-pharmacological interventions.¹¹²

In our sample, the pain specialists did not appear to consider a referral to an interventional radiologist, while most radiologists had performed only relatively few embolisations in their career. From this we cannot infer that a lack of referrals is the factor limiting the number of procedures undertaken, although the uncertainty and controversy around the definition of PCS is considered contributory by radiologists, from their open comments in the survey, and reflects our findings in *Chapter 3*. In the studies reviewed in *Chapter 6*, approximately half of the women were embolised using coils, and this method dominates UK practice.

There is a degree of discordance between the extent of symptomatic improvement cited in the observation studies discussed in *Chapter 6* and the beliefs of radiologists in the UK. The review revealed a pooled estimate of 75% achieving complete or significant improvement, while radiologists put an average of 38% probability of this outcome. That they anticipated a 20% risk of no benefit from embolisation possibly suggests a belief either that some women are refractory to this treatment or that there is not a complete association between PVI and CPP. It also hints at publication bias in the literature, if these beliefs reflect radiologists' experiences.

What the distribution of beliefs does clearly show is that there is uncertainty regarding the effectiveness of embolisation; this was supported by the overwhelming majority of radiologists, who thought that there was insufficient evidence and that a randomised trial was needed. This was echoed by the members of the support group, although, given the general lack of awareness of the condition, this may reflect a higher level of knowledge among those who do respond. Challenges facing any potential future research are substantial, given the prevalence, the diagnostic criteria, the attitude of specialists for referral and the potentially limited number of radiologists offering the procedure, but there appears to be an appetite for further research.

Chapter 8 Discussion

Introduction

We have addressed the commissioning brief, which asked for a review of the evidence on the relationship between refluxing pelvic veins and pelvic pain syndromes and the effectiveness of embolisation of refluxing veins.

We have completed the following discrete reviews and surveys as part of this project:

- a review of the terminology, definitions and criteria used in the description and diagnosis of PCS
- a review of the evidence regarding the association between radiological observations of dilated and/or refluxing pelvic veins and the symptoms of CPP
- a systematic review of the accuracy of ultrasound and MRI in determination of PVI, compared with venography
- a systematic review of the effectiveness of embolisation of incompetent pelvic veins
- a survey of the clinical practice of UK and international pain specialists and interventional radiologists with respect to the diagnosis and management of PCS, including the latter group's prior beliefs regarding the effectiveness of embolisation for PCS
- a survey of members of a pelvic pain support group to assess the lay awareness and understanding of PCS
- an opinion from interventional radiologists and support group members on the desirability of a RCT of pelvic vein embolisation.

Each of the reviews and surveys has been described in detail, the main findings have been reported and the conclusions have been derived in the light of limitations of the contributing primary research at the end of each chapter. We were unable to accomplish the objective of performing an IPD meta-analysis, owing to the quality and heterogeneity of the data available. This chapter attempts to bring together the key findings, summarise the limitations and provide recommendations for further research.

Summary of principal findings

Review of diagnostic criteria and definitions

There was no single, clearly defined criterion for a diagnosis that was reported in all of the studies included in the review. The majority of studies cited pelvic pain, dilated OVs and venous reflux or congestion as principal features of PCS, but many did not give thresholds or further clarification or, where they did, were heterogeneous. There is a need for a globally accepted diagnostic standard for PCS, which would help to standardise clinical evaluation and facilitate comparisons of outcomes of treatment effectiveness.

We propose a potential template of diagnostic criteria based on the following criteria:

- CPP, considered by the woman to have an impact on her quality of life, > 6 months' duration, located in the pelvic region below the umbilicus
- delineation of the presence of dysmenorrhoea, dyspareunia and pain after prolonged standing, and a subjective ranking of the severity of each symptom
- presence or absence of visible varices
- presence or absence of pelvic vein variants
- OV dilatation
- reflux in pelvic veins, in terms of retrograde flow on Valsalva manoeuvre, delayed refilling time and filling of contralateral veins.

Further work is required to determine score weightings and cut-off values, and validation of a combined score in a prospective study.

Association review

Overall, there is a lack of well-designed case controlled studies to delineate the relationship between CPP, dilated pelvic veins and PVI. In the five case-control studies with appropriate data,^{6,16,23,41,77} the associations were generally fairly similar, with three studies showing statistically significant associations (odds ratios of between 31 and 117).^{6,16,77} The two smallest studies failed to reach statistical significance in the odds of association, perhaps because they were too small to detect a difference. The proportion of women found to have PVI who reported CPP ranged considerably, from 39% to 91%. Polycystic ovaries were observed more frequently in the group with CPP and PVI in two studies. The prevalence of PVI ranged considerably, although the majority of women with PVI had CPP. Conversely, in the four studies of asymptomatic women undergoing pelvic vein imaging for other reasons, no more than half had PVI, although again the prevalence ranged widely. Where lower-limb venous insufficiency was seen, between 60% and 77% of women also had pelvic varices.

Review of the accuracy of imaging tests

Transcatheter selective venography performed in a tilted position remains the gold standard for the determination of PVI and is an integral part of pelvic vein embolisation, and, therefore, remains an essential part of the diagnostic process. TVUS with Doppler has a place in the screening of women for pelvic varices, although the data on accuracy are limited. One study provided diagnostic accuracy parameters of 96% sensitivity (95% CI 92% to 99%) and 100% specificity (lower 99% CI 97%), with positive and negative predictive values of 100% and 94%, respectively.³⁶ Similarly, MR venography appears to have good accuracy, but accuracy data are limited to one study, suggesting 88% sensitivity and 67% specificity for identifying PVI in the OV.³⁸ Imaging modalities that demonstrate both venous dilatation and reflux are necessary.

Review of the effectiveness of embolisation

This systematic review of embolisation for pelvic congestion system found no high-quality studies, so all estimates of effectiveness are derived from presumed prospective case series; therefore, all findings should be interpreted cautiously in view of the high risk of biased contributory data. These series reported on 1308 women, the majority of whom were of reproductive age and parous, while approximately one-third of patients clearly had bilateral embolisation, with metal coil placement being the dominant technique.

Early substantial relief from pain symptoms was observed in approximately 75% of patients, which generally increased over time and was sustained. Where pain was measured on a visual analogue scale, statistically significant reductions following treatment were observed in all studies. Reintervention rates were generally low. Where measured, embolisation reduced the diameter of dilated veins to a significant degree, with minimal residual reflux.

There were few data on the impact on menstruation, ovarian reserve or fertility, but no concerns were noted. Transient pain was a common occurrence following foam embolisation, while there was a < 2% risk of coil migration.

We considered that the proposed IPD meta-analysis would not yield enough comparable, high-quality data to make any sophisticated analysis worthwhile and so we did not proceed with this.

Surveys of clinical practice and lay awareness of pelvic congestion syndrome

We undertook three surveys to get a broad perspective of current understanding and management of PCS, eliciting responses from those with a specialist interest in pelvic pain, from interventional radiologists and from women with CPP. From these surveys, a few key themes can be drawn out, perhaps most significantly that there are some dissenting opinions regarding PCS as a cause of CPP. First of all, there is variation between pain specialists and interventional radiologists in their approach to diagnosis, but it is obvious that surgical management does not appear to be favoured. The majority of interventional radiologists do not perform many, if any, embolisations for PVI and, although their confidence in the procedure is reasonably high, there is a desire to strengthen the evidence base. Even among women with CPP, fewer than half had any knowledge about PCS.

Strengths and limitations

Literature searching

The key strength of this overview is that two extensive, protocol-driven literature searches were undertaken, one specifically for diagnosis and the other for treatment, ensuring that the maximum number of appropriate studies was identified. We searched multiple databases, including those that focus on journals not indexed by MEDLINE or EMBASE, to locate studies not cited by previous reviews, and selection was undertaken by two reviewers. We could be criticised for not conducting a search specific to the review of the association between PVI and CPP, thereby potentially missing important citations, but we are confident that the breadth of the search strategies enabled the capture of all relevant studies. In screening several thousand citations for the accuracy and effectiveness reviews, we located all of the papers included in the association review. Moreover, in the process of reviewing the shortlisted studies for these other reviews, we scanned the reference list for additional relevant papers and did not locate any additional contemporary papers. We are, therefore, confident that we have located all relevant case-control studies, although we may have missed some studies which were primarily focused on lower-limb insufficiency with secondary considerations of the coexistence of PVI.

For the review of definitions, we took a selected subset of all possible studies, selected on the basis that they were included in the accuracy and effectiveness systematic reviews, for which, again, we could be criticised. In the process of screening citations for the other reviews, we did not locate a single publication in which a consensus diagnostic standard had been derived by valid methods and believe it is likely that the identification of diagnostic themes has reached data saturation.

In each review, the required data were prespecified to avoid selective outcome reporting. In the review of diagnostic definitions, we categorised the criteria to predetermined groups and adopted a strict policy of extracting the definition from the methods section of each report. In the accuracy review, we prespecified the reference standard for consistency. Although we initially proposed to include ovarian ligation in the review of the effectiveness of treatments, dropping this modality from the review will have no implications for the conclusions, as ligation is nowadays rarely performed.

Quality of primary studies

A quality appraisal of the selected studies was conducted for the reviews of association, accuracy and effectiveness, using appropriate, validated quality checklists. This enabled interpretation of the data in the light of the potential biases in the primary studies. The generally poor quality of the studies' methodology and the heterogeneity of studies, together with inadequate reporting of disaggregated data, result in our inability to perform meta-analysis in the association and accuracy reviews, and meant we were able to combine data for only one outcome in the effectiveness review.

For the association review, the six most pertinent studies were unfortunately of mixed methodological quality.^{6,16,23,41,77,78} They drew on clinically disparate populations and defined PVI inconsistently, and in the case-control studies there was no matching on important confounders such as parity.

In the accuracy review, there were no concerns about the reference standard used in the selected studies. However, there were several issues common to most studies that undermine their estimates of accuracy. Only 2 of the 12 studies were prospective^{23,38} and included consecutive women, while in about half of the studies ultrasound was being used as a triage test to identify those women who would go on to have embolisation; consequently, those who did not show evidence of PVI on ultrasound never had the reference standard venography. Only the two studies attempted to blind the index test and only one of these was rigorous in its methods to prevent ascertainment bias in the analysis of the images.⁴⁰

The most significant limitation of the effectiveness review is the absence of randomised data. Only one RCT of embolisation is reported in the literature, and this was considered at risk of potential biases. The majority of the studies were relatively small case series, with no comparative group and frequently ill-defined inclusion criteria. We attempted to restrict the studies included to those in which participants were prospectively enrolled, to reduce selection bias, but in some studies it was impossible to be completely certain from the methodology that included participants were not retrospectively identified from medical records in some studies reviewed.

The effect of embolisation on pain was generally described either in terms of symptomatic improvement or as pain scores, reducing the amount of information available for either outcome. Given the general low quality of studies and the extreme variability of patient-reported outcomes, assessment points and participating characteristics in this systematic review, we did not collect IPD from the included studies in an attempt to improve the analysis.

All three surveys were limited in size and so may be unrepresentative. It was not possible to compare any characteristics of responders and non-responders. For the questions where frequencies were ranked, in retrospect it would have been of benefit to require a response for each question, so that the relative proportions were comparable. We were not able to elicit beliefs about the effectiveness of embolisation in a way that would provide a subjective probability for a range of potential effects.

Public and patient involvement

We have been supported throughout the project by the PPSN and, in particular, its chairperson. Unlike primary research, during which public and patient involvement can be crucial in improving the acceptability of a clinical trial and promoting recruitment, systematic reviews are more insular projects. This notwithstanding, we engaged with the PPSN chairperson throughout, developing an appreciation of the confusion and uncertainty surrounding PCS among women as well as the opinions of clinicians that the chairperson had encountered. This prompted us to extend the survey of clinical practice to include a survey targeted at women with CPP. We believed it important to establish a baseline estimate of the awareness of PCS, its diagnosis and management, and so we designed the survey in collaboration with the PPSN. The survey was circulated via the group's e-mail distribution list and, although the response rate was low, it provided useful information. The women who completed the survey were particularly aware that one specific symptom associated with a PCS diagnosis was pain made worse by long periods of standing. We highlight this as a particular question that could be posed to women during their clinical history taking. The main findings are, however, that there was little awareness of PCS as a potential diagnosis on the spectrum of disorders and that the majority of women welcomed further research.

We will engage with the PPSN regarding the dissemination of our findings, providing a plain English summary of symptoms, the potential treatment and the uncertainties around the evidence we have discussed here. This will be distributed via the PPSN's website and e-newsletter. Any future research groups taking forward the research recommendations from this project would benefit from engaging with the PPSN.

Conclusion

The data supporting the diagnosis and treatment of PVI in the presence of CPP are limited and of poor quality, and considerable further high-quality research is required to thoroughly address the research question. There is some evidence to tentatively support several of the required criteria which would indicate a causative association, but it cannot be stated that PVI is the cause of CPP in women with no other pathology, a conclusion echoed in some dissenting views among the clinical community. Transvaginal Doppler ultrasound and MR venography are widely used and useful screening methods but, ultimately, cannot replace conventional venography if embolisation is planned.

Implications for health care

There exist a proportion of women for whom no cause for their pain can be found at laparoscopy; this causes anxiety for the patient, and the search for a diagnosis can be protracted, placing a significant demand on health-care resources. The strength of the evidence with respect to diagnosis and management is insufficient for any clinical recommendations to be made, but some good-practice points can be listed. When taking a clinical history, gynaecologists should ask about specific pain symptoms, including whether or not pain is more severe after periods of standing and if it is relieved by lying down. During examination of the patient, the presence of vulval and lower-limb varicose veins should be noted. Transvaginal Doppler ultrasound should be made available for women exhibiting symptoms indicative of PVI. If this technique identifies incompetent pelvic veins, the radiologist can discuss the possibility of PCS as a diagnosis with her gynaecologist, highlighting the uncertainty in the data. If there are interventional radiologists available who perform embolisation of pelvic veins, a referral may be considered. Women should be counselled that the embolisation, although apparently safe, may not provide complete relief of symptoms. There are no robust data on clinical effectiveness and cost-effectiveness, so under current guidelines from the National Institute for Health and Care Excellence it not possible to state whether or not embolisation provides value for money.

Recommendations for research

There is scope for considerable further research, with robust methodology and of adequate size, into the condition known as PCS. The question of the association of PVI and CPP requires a well-powered case-control study, in which women with CPP are matched, using age and/or parity, to two or more pain-free controls. All women would need to provide a standardised account of their pain symptoms, their gynaecological and obstetric history, and be examined for vulval or lower-limb varicose veins, before undergoing a consistent TVUS assessment using the most modern Doppler technology. Interpretation of the ultrasound and Doppler data should be undertaken in duplicate, with readers blind to each other's assessments, to determine interobserver reliability. Ideally, a small subsample of patients should have the same ultrasound procedure performed at two time points, to assess if timing in relation to the menstrual cycle is important, and to assess intraobserver consistency. This would provide data on the odds of PVI being associated with CPP and on the reproducibility of ultrasound protocol.

This potential association study is predicated on there being a clear definition of PVI, but it will also provide data to derive the diagnostic performance of each individual criterion, in terms of the ability to discriminate PCS from pain-free controls. For example, a receiver operating curve for OV dilatation could be produced, using various thresholds to define dilatation, and the optimum cut-off value could be obtained. Those parameters with a statistically significant difference between the CPP and pain-free groups of women would be incorporated into a logistic regression model. The regression coefficients of the best-fit model could be used to weight scores for each criterion before summation to a combined score.

A further study of women who were prepared to have TVUS with Doppler and conventional venography would be required to provide the threshold for the total score, in addition to reliably determining the accuracy of TVUS with Doppler, again mapping the score on a receiver operating curve to determine the cut-off value that provides the optimum clinical performance with respect to sensitivity and specificity. Finally, the scoring system would be validated in a prospective study of women with CPP to determine its accuracy. This would then provide a practical, valid tool for clinical use that would assist in the identification of women for invasive confirmatory venography and, potentially, treatment of PCS.

Assuming a clear diagnostic standard for PCS can be obtained in this method, there remains the issue of whether or not embolisation is an effective treatment. An adequately powered randomised trial is essential to provide the necessary data, but faces methodological challenges. Pain is a subjective phenomenon and prone to measurement bias unless a placebo or sham intervention is provided. In a previous study of a neuroablative technique for CPP, women who were blinded to whether they had the procedure or a sham equivalent all reported an improvement in pain to a comparable extent.¹¹³ A conventional venogram would be required to verify PVI immediately prior to randomisation between a legitimate or a sham embolisation. How the blinding of the woman can be maintained, with the woman only under sedation, is potentially challenging, but it is ethical given its necessity in reducing the risk of bias and the low risk of complications from venography. There are no precedents found in the use of sham embolisation from the equivalent male condition of spermatic vein varicocele, as in this condition the intention is to improve subfertility, whereas pregnancy rates can be objectively ascertained.

Finally, an economic evaluation of the diagnostic pathway and of embolisation would provide the final evidence of whether or not the proposed management strategy is cost-effective. It would be of general benefit in the area of CPP to collect information on overall and condition-specific quality of life and on the quantity and type of health-care resources consumed by women, as there are few contemporary data in this field.

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Contributions of authors

Rita Champaneria, systematic reviewer, Birmingham Clinical Trials Unit, University of Birmingham, designed and performed the literature searches, identified and retrieved all relevant papers, and contributed to the writing of this report.

Laila Shah, research administrator, Birmingham Clinical Trials Unit, University of Birmingham, maintained detailed records of citations identified by literature searches, retrieved relevant papers, extracted data and tabulated results.

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Data sharing statement

Data obtained via literature searches in the production of this report can be obtained from the corresponding author.

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Appendix 1 Search strategies

Search strategies for population and diagnosis

Date range searched for all databases: inception to March 2014.

African Index Medicus

Search strategy

pelvic AND congestion

reflux AND vein

Cumulative Index to Nursing and Allied Health Literature

Search strategy

pelvic AND congestion AND imaging

reflux AND veins AND chronic pelvic

reflux AND veins AND imaging

The Cochrane Library

Search strategy

#1 chronic pelvic pain

#2 CPP

#3 chronic

#4 pelvic pain

#5 pelvic adj2 pain

#6 #4 or #5

#7 pain

#8 #3 and #6 and #7

#9 dyspareunia

#10 dysmenorrhoea

#11 dysmenorrhea

#12 #10 or #11

#13 #1 or #2 or #8 or #9 or #12

- #14 ultrasonography
- #15 ultrasound
- #16 ultrasonic
- #17 doppler
- #18 sonography
- #19 #14 or #15 or #16 or #17 or #18
- #20 magnetic resonance imaging
- #21 magnetic resonance imag*
- #22 mri
- #23 #20 or #21 or #22
- #24 tomography, x-ray computed
- #25 cat scan
- #26 catscan
- #27 comput* adj2 tomog*
- #28 CT 37,169
- #29 #24 or #25 or #26 or #27 or #28
- #30 angiography
- #31 angiogra*
- #32 phlebography
- #33 venography
- #34 #19 or #23 or #29 or #30 or #31 or #32 or #33
- #35 #13 and #34

Database of Abstracts of Reviews of Effects

Search strategy

pelvic congestion AND reflux vein

chronic pelvic pain AND pelvic congestion

reflux vein AND imaging

EMBASE

Date range: 1980 to week 9 2014.

1. chronic pelvic pain.mp.
2. CPP.mp.
3. chronic.mp.
4. exp pelvic pain/
5. pelvic pain.mp.
6. (pelvic adj2 pain).mp.
7. 4 or 5 or 6
8. exp pain/
9. pain.mp.
10. 8 or 9
11. 3 and 7 and 10
12. exp dyspareunia/
13. dyspareunia.mp.
14. 12 or 13
15. exp dysmenorrh\$ea/
16. dysmenorrh\$ea.mp.
17. 15 or 16
18. 1 or 2 or 11 or 14 or 17
19. exp ultrasonography/
20. ultrasonography.mp.
21. exp ultrasound/
22. ultrasound.mp.
23. exp ultrasonic/
24. ultrasonic.mp.
25. doppler.mp.
26. exp sonography/
27. sonography.mp.
28. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp magnetic resonance imaging/
30. magnetic resonance imag*.mp.
31. exp mri/
32. mri.mp.
33. 29 or 30 or 31 or 32
34. exp tomography, x-ray computed/
35. tomography, x-ray computed.mp.
36. exp cat scan/
37. catscan.mp.
38. cat scan.mp.
39. exp comput*/ adj2 tomog*/
40. (comput* adj2 tomog*).mp.
41. CT.mp.
42. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43. exp angiography/
44. angiogra*.mp.
45. 43 or 44
46. exp phlebography/
47. phlebography.mp.
48. 46 or 47
49. exp venography/
50. venography.mp.

- 51. 49 or 50
- 52. 28 or 33 or 42 or 45 or 48 or 51
- 53. 18 and 52

Index Medicus for the Eastern Mediterranean Region (IMEMR)

Search strategy

reflux AND vein

Index Medicus for the South-East Asian Region (IMSEAR)

Search strategy

reflux pelvic pain

reflux pelvic vein imaging

chronic pelvic pain reflux pelvic pain

Latin American and Caribbean Health Sciences Literature (LILACS)

Search strategy

reflux vein AND chronic pelvic pain

reflux vein AND chronic pelvic pain AND imaging

MEDLINE [Ovid MEDLINE(R)]

Date range: 1946 to week 3, February 2014.

Search strategy

1. chronic pelvic pain.mp.
2. CPP.mp.
3. chronic.mp.
4. exp pelvic pain/
5. pelvic pain.mp.
6. (pelvic adj2 pain).mp.
7. 4 or 5 or 6
8. exp pain/
9. pain.mp.
10. 8 or 9
11. 3 and 7 and 10
12. exp dyspareunia/
13. dyspareunia.mp.
14. dysmenorrh\$ea.mp.
15. 1 or 2 or 11 or 12 or 13 or 14
16. exp ultrasonography/
17. ultrasonography.mp.
18. ultrasound.mp.
19. exp ultrasonic/
20. ultrasonic.mp.
21. doppler.mp.
22. sonography.mp.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. exp magnetic resonance imaging/
25. magnetic resonance imag*.mp.
26. mri.mp.
27. 24 or 25 or 26
28. exp tomography, x-ray computed/
29. catscan.mp.
30. cat scan.mp.
31. (comput* adj2 tomog*).mp.
32. CT.mp.
33. 28 or 29 or 30 or 31 or 32
34. exp angiography/
35. angiogra*.mp.
36. 34 or 35
37. exp phlebography/
38. phlebography.mp.
39. 37 or 38
40. exp venography/
41. venography.mp.
42. 40 or 41
43. 23 or 27 or 33 or 36 or 39 or 42
44. 15 and 43

Pan American Health Organisation

Search strategy

pelvic AND congestion

reflux AND vein

Population Information Online

Search strategy

chronic pelvic pain AND reflux pelvic vein AND imaging

reflux vein

chronic pelvic pain AND pelvic congestion syndrome

reflux vein AND 'imaging

Scientific Electronic Library Online

Search strategy

reflux vein AND imaging

Web of Science

Search strategy

#1 TS=chronic pelvic pain

#2 TS=CPP

#3 TS=chronic

- #4 TS=pelvic pain
- #5 TS=pelvic
- #6 #4 OR #5
- #7 TS=pain
- #8 #3 And #6 AND #7
- #9 TS=dyspareunia
- #10 TS=dysmenorrhoea
- #11 TS=dysmenorrhea
- #12 #10 OR #11
- #13 #1 OR #2 OR #8 OR #9 OR #12
- #14 TS=ultrasonography
- #15 TS=ultrasound
- #16 TS=ultrasonic
- #17 TS=doppler
- #18 TS=sonography
- #19 #14 OR #15 OR #16 OR #17 OR #18
- #20 TS=magnetic resonance imaging
- #21 TS=mri
- #22 #20 OR #21
- #23 TS=tomography, xray computed
- #24 TS=cat scan
- #25 TS=catscan
- #26 TS=comput*/ adj2tomog'/
- #27 TS=comput* adj2tomog*
- #28 TS=comput* tomog*
- #29 TS=computer tomography
- #30 TS=CT

#31 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30

#32 TS=angiography

#33 TS=angiogram*

#34 #32 OR #33

#35 TS=phlebography

#36 TS=venography

#37 #19 OR #22 OR #31 OR #34 OR #35 OR #36

#38 #13 AND #37

Western Pacific Region Index Medicus

Search strategy

reflux pelvic vein imaging

reflux pelvic vein

Search strategies for population and treatment

Date range searched for all databases: inception to September 2013.

Bioscience Information Service Web of Knowledge

Search strategy

#1 TS=pelvic pain

#2 TS=chronic pelvic pain

#3 TS=CPP

#4 TS=pelvic congestion

#5 TS=PCS

#6 TS=congestion syndrome

#7 TS=pelvic congestion syndrome

#8 TS=pelvic venous incompetence

#9 TS=PVI

#10 TS=ovarian vein incompetence

#11 TS=((pelvic or pelvis or iliac or ovarian) adj (vein\$ or varices))

#12 TS=(reflux& or incompetence)

#13 #12 AND #11

#14 #3 AND #2 AND #1

#15 #7 AND #6 AND #5 AND #4

#16 #9 AND #8

#17 #16 OR #15 OR #14 OR #13 OR #10

#18 TS=treatment

#19 TS=therap\$

#20 TS=emboli*ation

#21 TS=sclerotherapy

#22 TS=sc*lerotherapy

#23 TS=ligation

#24 TS=interventional radiology

#25 TS=therapeutic emboli*ation

#26 TS=balloon occlusion

#27 TS=occlusion

#28 TS=dilatation

#29 TS=vasculari*ation

#30 TS=endovascular surgery

#31 TS=laparoscopic surgery

#32 TS=vascular surgical procedure

#33 TS=vascular surgery

#34 TS=embolotherapy

#35 #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18

#36 #35 AND #17

British Nursing Index

Searched for: all (pelvic congestion)

Cumulative Index to Nursing and Allied Health Literature

Search strategy

S1 TX=pelvic congestion

S2 TX=PCS

S3 TX=congestion syndrome

S4 TX=pelvic congestion syndrome

S5 TX=S1 OR S2 OR S3 OR S4

S6 TX=treatment

S7 TX=therapy

S8 TX=emboli*ation

S9 TX=embolisation

S10 TX=embolization

S11 TX=sclerotherapy

S12 TX=sc*lerotherapy

S13 TX=ligation

S14 TX=balloon occlusion

S15 TX=occlusion

S16 TX=dilatation

S17 TX=vasculari*ation

S18 TX=endovascular surgery

S19 TX=laparoscopic surgery

S20 TX=embolotherapy

S21 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20

S22 S5 AND S21

The Cochrane Library

Search strategy

Pelvic congestion AND PCS search – HTAs

Pelvic congestion AND PCS search – trials

reflux AND vein search – Cochrane reviews

reflux AND vein search – HTAs

reflux AND vein search – Other reviews

reflux AND vein search – trials

Database of Abstracts of Reviews of Effects

Search strategy

pelvic congestion

reflux AND vein

EMBASE

Search strategy

Date range: 1980 to week 14 2013.

1. exp Pelvic pain/ or chronic pelvic pain.mp.
2. CPP.mp.
3. pelvic congestion.mp.
4. PCS.mp.
5. congestion syndrome.mp.
6. pelvic congestion syndrome.mp.
7. pelvic venous incompetence.mp.
8. PVI.mp.
9. ovarian vein incompetence.mp.
10. ((pelvic or pelvis or iliac or ovarian) adj (vein\$ or varices)).mp.
11. (reflux\$ or incompetence).mp.
12. 10 and 11
13. 1 and 2
14. 3 and 4
15. 3 and 4 and 5 and 6
16. 7 and 8
17. 9 or 12 or 13 or 15 or 16
18. treatment.mp.
19. therap\$.mp.
20. emboli*ation.mp.
21. exp Sclerotherapy/ or sc*lerotherapy.mp.
22. ligation.mp. or exp ligation/
23. interventional radiology.mp. or exp Radiology, Interventional/
24. exp Embolization, therapeutic/ or balloon occlusion.mp.
25. occlusion.mp.
26. dilatation.mp. or exp Dilatation/

27. vasculari*ation.mp.
28. endovascular surgery.mp.
29. laparoscopic surgery.mp.
30. exp Vascular Surgical Procedures/ or vascular surgery.mp.
31. embolotherapy.mp. or exp Embolization, therapeutic/
32. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 17 and 32

Index Medicus for the Eastern Mediterranean Region

Search strategy

pelvic congestion

reflux vein

Index Medicus for the South-East Asian Region

Search strategy

pelvic congestion syndrome

Index of Scientific and Technical Proceedings

Pelvic congestion syndrome AND vein

Latin American and Caribbean Health Sciences Literature

Search strategy

pelvic AND congestion

reflux AND vein

Medion

Search strategy

pelvic AND congestion

reflux AND vein

MEDLINE [Ovid MEDLINE(R)]

Date range: 1946 to week 1, March 2013.

Search strategy

1. exp Pelvic Pain/ or chronic pelvic pain.mp.
2. CPP.mp.
3. pelvic congestion.mp.
4. PCS.mp.
5. congestion syndrome.mp.
6. pelvic congestion syndrome.mp.
7. pelvic venous incompetence.mp.
8. PVI.mp.
9. ovarian vein incompetence.mp.
10. ((pelvic or pelvis or iliac or ovarian) adj (vein\$ or varices)).mp.
11. (reflux\$ or incompetence).mp.

12. 10 and 11
13. 1 and 2
14. 3 and 4
15. 3 and 4 and 5 and 6
16. 7 and 8
17. 9 or 12 or 13 or 15 or 16
18. treatment.mp.
19. therap\$.mp.
20. emboli*ation.mp.
21. exp Sclerotherapy/ or sc*lerotherapy.mp.
22. ligation.mp. or exp Ligation/
23. interventional radiology.mp. or exp Radiology, Interventional/
24. exp Embolization, Therapeutic/ or balloon occlusion.mp.
25. occlusion.mp.
26. dilatation.mp. or exp Dilatation/
27. vasculari*ation.mp.
28. endovascular surgery.mp.
29. laparoscopic surgery.mp.
30. exp Vascular Surgical Procedures/ or vascular surgery.mp.
31. embolotherapy.mp. or exp Embolization, Therapeutic/
32. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. 17 and 32

Pan American Health Organisation

Search strategy

pelvic AND congestion

pelvic AND congestion AND syndrome

reflux AND vein

Population Information Online

Search strategy

pelvic congestion syndrome

pelvic congestion

reflux vein

Scientific Electronic Library Online

Search strategy

pelvic AND congestion AND syndrome

reflux AND vein

pelvic congestion

Web of Science

Search strategy

#1 TS=pelvic pain

#2 TS=chronic pelvic pain

#3 TS=CPP

#4 TS=pelvic congestion

#5 TS=PCS

#6 TS=congestion syndrome

#7 TS=pelvic congestion syndrome

#8 TS=pelvic venous incompetence

#9 TS=PVI

#10 TS=ovarian vein incompetence

#11 TS=((pelvic or pelvis or ovarian) adj (vein\$ or varices))

#12 TS=(9reflux\$ or incompetence)

#13 #12#AND #11

#14 #3 AND #2 AND #1

#15 #7 AND #6 AND #5 AND #4

#16 #9 AND #8

#17 #16 OR #15 OR #14 OR #13 OR #10

#18 TS=treatment

#19 TS=therap\$

#20 TS=emboli*ation

#21 TS=sclerotherapy

#22 TS=sc*lerotherapy

#23 TS=ligation

#24 TS=interventional radiology

#25 TS=therapeutic emboli*ation

#26 TS=balloon occlusion

#27 TS=occlusion

#28 TS=dilatation

#29 TS=vasculari*ation

#30 TS=endovascular surgery

#31 TS=laparoscopic surgery

#32 TS=vascular surgical procedure

#33 TS=vascular surgery

#34 TS=embolotherapy

#35 #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18

#36 #35 AND #17

Western Pacific Region Index Medicus

Search strategy

pelvic congestion

reflux vein

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

**EME
HS&DR
HTA
PGfAR
PHR**

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