EXPLORING A VASCULAR CAUSE FOR CHRONIC PELVIC PAIN IN WOMEN

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD) in the Faculty of Biology Medicine and Health

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<th>Description</th>
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<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CPP</td>
<td>Chronic pelvic pain</td>
</tr>
<tr>
<td>EQ-5D-3L</td>
<td>Euroqol quality of life measure, 3-Level</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>LR</td>
<td>Likelihood Ratio</td>
</tr>
<tr>
<td>MPQ</td>
<td>McGill Pain Questionnaire</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Clinical Excellence</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute of Healthcare Research</td>
</tr>
<tr>
<td>OR</td>
<td>Odd's Ratio</td>
</tr>
<tr>
<td>PCS</td>
<td>Pelvic congestion syndrome</td>
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<tr>
<td>PVI</td>
<td>Pelvic vein incompetence</td>
</tr>
<tr>
<td>RCOG</td>
<td>Royal College of Obstetrics and Gynaecology</td>
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<tr>
<td>RCT</td>
<td>Randomised control trial</td>
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<tr>
<td>SF-MPQ</td>
<td>Short-Form McGill Pain Questionnaire</td>
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<tr>
<td>TVU</td>
<td>Trans-vaginal ultrasound</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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THESIS ABSTRACT

EXPLORING A VASCULAR CAUSE FOR CHRONIC PELVIC PAIN IN WOMEN OF CHILDBEARING AGE

Vivak Hansrani, Doctor of Philosophy (PhD), The University of Manchester, 2016

Objectives: Pelvic vein incompetence (PVI) has been suggested as a cause for chronic pelvic pain. The overall objective of this thesis is to determine how PVI affects women, identify suitable methods of diagnosis and provide evidence regarding its association with chronic pelvic pain. This thesis will also evaluate the evidence behind its treatment.

Methods: Four observation studies were completed during this thesis. A characterisation study encompassing 120 participants was performed to determine symptoms commonly experienced by women with PVI. Two observation studies analysed the ability of trans-vaginal ultrasound to detect PVI and compared its accuracy with reflux venography; considered the reference standard. A further 70 participants were recruited in a case-control study to determine the prevalence of PVI in women with and without chronic pelvic pain. A randomised control trial treating women with PVI and pelvic pain was also designed.

Results: Women with PVI had an increased frequency of CPP when compared with healthy controls or women with varicose veins. This pain was associated with the menstrual cycle and intercourse. It was also found to frequently radiate into the upper thighs. Trans-vaginal ultrasound was shown to have a sensitivity and positive predictive value of 100% and 95% respectively when compared with reflux venography. The frequency of PVI in women with chronic pelvic pain was found to be 47% compared with 25% in women with no history of CPP (p<0.001).

Conclusion: The results of this thesis suggest PVI to be a possible cause of CPP in women and likely to be under-diagnosed. It can be identified by trans-vaginal ultrasound although the degree of accuracy is still yet to be determined. PVI merits further research and attention from clinicians and researchers. The proposed randomised control trial is needed both to further understanding of the role of PVI in CPP and to assess the efficacy of an under-researched treatment approach currently used in practice.
DECLARATION

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.
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ACKNOWLEDGEMENTS

I will always look back at my time in the Academic Surgery Unit very fondly. First and foremost I would like to express my sincere appreciation and thanks to Professor Charles McCollum and Professor Ann Caress who gave me the opportunity to work within the unit and guided me throughout the process. Their encouragement, guidance and advice has been invaluable in my development. I am also very grateful to Mr Mourad Seif for his advice and guidance on conducting research in women's health. I would also like to thank my colleagues Angela, Eric, Josh, Clare and the rest of the team who made the whole experience fun!

Finally I would like to thank my parents and my wife Punam who have always been behind me and supported me throughout this process and everything else that I do.
RATIONALE FOR SUBMITTING THE THESIS IN THE ALTERNATIVE FORMAT

The rationale for submitting this thesis in an alternative format was because the programme of research has been designed as several individual studies on a common theme which each provide new evidence on pelvic vein incompetence that is expected to be published in peer-reviewed journals.

It was agreed among the supervisory team that the alternative format would be appropriate for this programme of work and my objective was to produce and submit manuscripts for completed sections of this work early on in the programme. Subsequently, this thesis currently includes two papers which are published in the European Journal of Obstetrics and Gynaecology, a third paper published in Vascular and a further chapter published in the ISRCTN Registry (BioMed Central). Two further manuscripts have been prepared for submission in peer-reviewed medical journals.
CHAPTER 1: CHRONIC PELVIC PAIN

Introduction
Chronic pelvic pain (CPP) is widely accepted as a major health problem, and was prioritised for research by the National Institute of Healthcare Research (NIHR) in 2012. It is a vague term that can be used to address a symptom or a syndrome in its own right. The Royal College of Obstetrics and Gynaecologists (RCOG) define CPP as ‘continuous or intermittent lower abdominal pain of at least six months duration not occurring exclusively with menstruation, intercourse or pregnancy’.1
CPP can incorporate a variety of symptoms such as pain occurring during or after sexual intercourse (dyspareunia), painful bowel motions (dyschesia), pain on passing urine (dysuria) and painful periods (dysmenorrhoea).2 Associated features not related to the pelvis or abdomen but commonly seen in relation to CPP include headaches, nausea, depression, sleep disturbance and fatigue.3

CPP commonly affects younger women and living with any chronic pain carries a heavy economic and social burden. It is a leading cause of social isolation, marital discord and loss of employment in women. The prevalence of CPP in women is difficult to ascertain as its definitions vary and many women do not seek medical advice. In the primary care setting amongst women aged between 12-70 years, CPP has an annual prevalence of 38 per 1000. This was found to be comparable to the prevalence of asthma (37/1000) and chronic back pain (41/1000).4 The worldwide prevalence of CPP is thought to be as high as 24% of the female population, but is difficult to determine as there are few valid population based estimates of disease burden from less developed countries.5 Many women with CPP in fact do not consult their doctor, with UK community-based studies demonstrating that approximately 41% of women with CPP failed to seek help about their symptoms; often anxiety being the most common reason.6 7 CPP currently accounts for between 20-40% of all gynaecology outpatient appointments, and 5% of all new referrals.8 9 Many women undergo invasive investigations with over 40% of all laparoscopies performed in the UK being for CPP diagnosis.8
The economic burden of CPP is substantial. Over 18% of employed women report taking one day off a year due to CPP. Direct NHS treatment costs in the UK were estimated to be £182 million/year in 1992 which is likely to be substantially higher now. Direct costs of healthcare in the United States estimated from Medicare tariffs (and hence very conservative) were $881.5 million. Patient out-of-pocket expenses were estimated at $1.9 billion and indirect costs due to time off work were estimated at $555.3 million.

Often referred to as ‘heart sink’ patients CPP in women is difficult to diagnose and treat. May women have self-limiting CPP with cohort studies showing that after nearly three and half years 25% of women with CPP recover without intervention. These findings of self-limiting CPP symptoms have also been seen in RCTs from patients with CPP allocated to a no treatment or placebo arm. Improvements in pain have not been shown to be related to any demographic or clinical characteristic measured at baseline and a similar phenomenon has been observed in irritable bowel syndrome and chronic fatigue syndrome.

Causes of chronic pelvic pain
Common causes of CPP in women of childbearing age include endometriosis, pelvic inflammatory disease, adhesions, irritable bowel syndrome, interstitial cystitis, musculoskeletal and nerve-related pain (table 1). Social, psychological and emotional factors have been reported to be associated with the development CPP. This included sexual abuse, anxiety, depression, drug or alcohol abuse and psychological comorbidity. Over 40% of women with CPP fail to obtain a diagnosis for their symptoms, with around 55% having no obvious organic cause seen on diagnostic laparoscopy.

Careful history and physical findings will commonly reveal causes for CPP that can therefore be treated quickly. For example changes in pain symptoms over the menstrual cycle and on sexual intercourse may well be endometriosis or adenomyosis. A clinical examination combined with trans-vaginal ultrasound is effective at identifying ovarian pathology. Vascular adhesions can cause pain by organ distension and stretching and evidence of improved symptoms after division
is present. However fine adhesions are commonly thought to be asymptomatic and laparoscopic division has not been shown to improve pain symptoms.\textsuperscript{20} Observational studies have indicated that endometriosis could have an incidence as high as 80%. This has led to a change of view from ‘why do some women develop endometriosis into ‘why does endometriosis develop into a pathological condition in some women.’ This does suggest that endometriosis can exist without causing pelvic pain or infertility.\textsuperscript{21} While in general there is no established relationship between the extent of the disease and symptoms, the location and type of the disease can impact pelvic pain.

Damage to peripheral nerves following surgery, trauma, inflammation or infection can be a common cause for CPP. This ‘neuropathic pain’ is often (but not always) characterised by burning, aching and shooting pain sensations. Local neurochemical factors such as tumour necrosis factor alpha (TNF-\(\alpha\)) and chemokines have also been shown to cause hyper-stimulation of normally quiescent fibres resulting in altered and heightened sensation and pelvic pain symptoms.\textsuperscript{22-24}

As many as 50\% of women referred to gynaecology clinics have symptoms suggestive of irritable bowel syndrome and 40\% with symptoms suggestive of interstitial cystitis.\textsuperscript{25 26} Musculoskeletal pain may also be a primary source of CPP in women. Pelvic floor myalgia, pain from joints or injury to the abdominal wall muscles have also been reported as causes.\textsuperscript{21 22}
### Table 1 Differential diagnosis of chronic pelvic pain

<table>
<thead>
<tr>
<th><strong>Gynaecology</strong></th>
<th><strong>Gastroenterology</strong></th>
<th><strong>Urology</strong></th>
<th><strong>Musculoskeletal</strong></th>
<th><strong>Neurology</strong></th>
<th><strong>Psychological</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>Irritable bowel syndrome</td>
<td>Interstitial cystitis</td>
<td>Pelvic floor myalgia</td>
<td>Neuralgia of ilioinguinal, genitofemoral, pudendal nerves</td>
<td>Major depression</td>
</tr>
<tr>
<td>Chronic pelvic inflammatory disease</td>
<td>Inflammatory bowel disease</td>
<td>Recurrent urinary tract infections</td>
<td>Myofascial pain</td>
<td>Neuropathic pain</td>
<td>Somatization</td>
</tr>
<tr>
<td>Pelvic varicosities</td>
<td>Diverticular disease</td>
<td>Urethral diverticulum</td>
<td>Piriformis syndrome</td>
<td>Abdominal migraine</td>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Fibroids</td>
<td>Chronic constipation</td>
<td></td>
<td>Psoas inflammation</td>
<td></td>
<td>Physical, sexual or substance abuse</td>
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<td>Ovarian cysts</td>
<td>Hernia</td>
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<td>Sacroiliac joint inflammation</td>
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<td>Adhesions</td>
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<td>Fibromyalgia</td>
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<td>Uterine prolapse</td>
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<td>Adenomyosis</td>
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#### Diagnosis

**Diagnostic pathway and clinical assessment**

Women with CPP symptoms are often referred to a gynaecologist by their general practitioner (GP) once any obvious infective or alternative organic causes of their pain symptoms have been excluded or treated. A diagnostic pathway for investigating and managing chronic pelvic pain is available from the RCOG Green Top Guidelines and from the European Association of Urology. The two guidelines have been combined to produce the diagnostic pathway shown in figure 1.127

Undertaking a detailed history and examination formulates the foundation of obtaining an accurate diagnosis. The International Pelvic Pain Society recommends the use of pain scores such as the visual analogue scale, body charts and the Short-Form McGill Questionnaire (SF-MPQ) to help patients convey the severity of their symptoms, and encourage clinicians to use this information to formulate a management plan.28 Although such tool help patients articulate their experiences,
scores such as the SF-MPQ have been shown to not capture the full experience and descriptions women attribute to pain.29

Figure 1 Diagnostic pathway for women with CPP

Chronic pelvic pain

History and physical examination

Symptoms and examination suggestive of gynaecological disease

Assessment: gynaecological examination, ultrasound, laparoscopy

Treat organic pathology identified according to specific disease guidelines

Multidisciplinary approach to persistent disease state

Hormonal therapy in well defined states

Psychological treatment

Symptoms and examination suggestive of non-gynaecological disease

Treat according to specific disease guidelines
Pelvic ultrasound

Trans-vaginal ultrasound is often the first investigation performed in women with CPP. It is an important part of assessment and has been shown to be effective at identifying fibroids, adenomyosis and differentiating endometriosis from other adnexal masses (figure 2).³⁰ ³¹ ³²

Trans-vaginal ultrasound performed before laparoscopy can identify soft markers of tenderness or poor ovarian mobility which has been shown to improve the pre-laparoscopy probability of identifying relevant pathology to over 70%. In the absence of soft markers on ultrasound, the laparoscopic likelihood of identifying pathology falls to 20%.³¹

Figure 2 Adenomyosis illustrated on trans-vaginal ultrasound

Laparoscopy

Laparoscopy is considered the gold standard diagnostic test for women with CPP.¹ It is reported to reliably identify endometriosis and adhesions; two of the most common causes for CPP (figure 3 and 4).¹ ³³
However it does carry risks, with an estimated risk of death being approximately 1/10,000 and injury to bowel, bladder or blood vessel being approximately 2.4/1000.8 34 35

Up to 55% of all diagnostic laparoscopies are negative, with much of the pathology identified not necessarily the cause of pain.19 36 Laparoscopy is also known to have a significant placebo effect despite no treatment being delivered.37 38

Women with CPP who are found to have no pathology on laparoscopy have limited treatment options and are often referred to allied specialities such as urology and gastroenterology and undergoing further invasive investigations.39 Frequently women who choose not to have any further children are often offered hysterectomy as a radical treatment with little evidence of benefit.40

Figure 3 Endometriosis and adhesions identified on laparoscopy
Management

Pharmacological management and alternative therapies for CPP

With the aetiology of CPP often being multifactorial, tailoring effective treatment plans is challenging. Analgesics are often the first line of management with many women managing their pain with over the counter preparations before consulting their doctor. Ovarian suppression using the combined oral contraceptive pill, progesterone, Danazol or GnRH analogues has been proven to be effective in cyclical pain possibly related to endometriosis. Surprisingly non-endometriosis-related cyclical pain has also been shown to be successfully controlled using these treatments.

Medroxyprogesterone Acetate (MPA), Lofexidine, Goserelin, Gabapentin and Amitryptyline have all been studied in clinical trials which were recently reviewed in a Cochrane review. The studies all suffered with significant design flaws from high attrition rates, lack of blinding, and many did not describe their randomisation procedures. Tricyclic antidepressants, Venlafaxine, Gabapentin and Amitryptyline have also been shown to reduce CPP symptoms in women but there is no current treatment ladder or pathway available for clinicians to determine which non-surgical intervention will work.
Non-medical (or alternative therapies) for CPP have been evaluated in several clinical studies. Writing about the stress of pelvic pain symptoms as a therapeutic intervention showed small positive differences in outcome.\textsuperscript{45} Counselling supported by ultrasound scanning after a negative laparoscopy was found to be effective at improving pain scores and mood in one RCT.\textsuperscript{46} Showing women photographs of findings at laparoscopy did not improve the immediate understanding and satisfaction with the consultation, nor show any benefit in symptoms when recorded using a visual analogue score.\textsuperscript{47}

It's clear that a combination of pharmacological intervention with counselling support may well be an effective mechanism of helping women with CPP manage their symptoms.

**Surgical management of CPP**

Surgical treatment for CPP is dependent on the organic cause for symptoms identified. Laparoscopic vaporisation or excision of endometrial stroma has been shown to reduce pain in women diagnosed with endometriosis.\textsuperscript{48} Adhesions can cause pain by organ distension or stretching. The division of dense, vascular adhesions was found to produce significant pain relief in one RCT,\textsuperscript{20} but no differences in pain scores were seen in other studies of women undergoing laparoscopic adhesiolysis compared with laparoscopy alone.\textsuperscript{25} \textsuperscript{49} Laparoscopic uterosacral nerve ablation (LUNA) has been shown to be ineffective in the management of CPP.\textsuperscript{19} \textsuperscript{50}

One study followed up 308 women who underwent hysterectomy for CPP over 12 months. Approximately 74\% of women experienced complete resolution of their pelvic pain symptoms but 26\% of the women experienced continued or even increased pain after hysterectomy.\textsuperscript{51}
Patient experiences of chronic pelvic pain

A recent meta-ethnography sought to gain a greater understanding of patient experiences of CPP. The study showed that CPP has a significant physical and emotional impact and may women are very focused on trying to obtain a medical diagnosis. Suffers often used the words anger, low mood, guilt, loss, anxiety, frustration, fear and dread when describing their thoughts about their symptoms and often describe a struggle to lead a normal life and fulfil their expected roles. Participants in the study often compared themselves to their healthy ‘real’ self before pain and felt they were unable to make future plans and goals leading to a sense of powerlessness.

Validation by diagnosis was another concept described by sufferers, which describes the need for a biomedical explanation. Having a diagnosis gave relief (i.e. It's not cancer) and validation. Those diagnosed with endometriosis felt vindicated after long delays, others felt angry for not being diagnosed sooner. Diagnosis sanctioned social support and gave hope, although hope was often short-lived if no effective treatment was available. The lack of medical evidence implied the pain was in their mind making women doubt their own experiences.

A large proportion of the women in the study felt invalidated by healthcare professionals. Pain was normalised by doctors who compared them with other women who ‘coped’. Women felt brushed away if not referred to specialists. Explanations such as ‘it will be OK when you're pregnant’ did nothing to alleviate suffering. Women felt their stories were not heard.

These results mirror similar findings in earlier research that demonstrated that women with CPP are significantly more likely to use dissociation as a coping mechanism for their pain. Common themes in research regarding the patient experience of CPP are the concerns regarding doctors negating the patients experience and the concept of CPP without organic pathology implying psychological problems.
Chapter summary

This chapter provides an outline of CPP in women, describing its common causes, methods of investigation and treatment. It also comments on patient experiences of dealing with CPP symptoms and the clinical course of the condition.

It is clear that CPP carries a significant physical, social and psychological burden and is a common cause of social isolation, loss of employment and marital discord. Around 40% of women with CPP will go on to have a diagnostic laparoscopy which is an invasive surgical procedure that is often normal in approximately 55% of cases. Even when pathology is found it is difficult to actually determine if it’s the actual cause of their symptoms. Those patients who do not have a biological cause identified are often re-referred to allied specialities such as gastroenterology and re-investigated. This convoluted clinical course is well documented and often leaves women with CPP disengaged and disheartened with the health care services.

There is strong evidence that a proportion of women with CPP have self-limiting symptoms that resolve over time. This makes conducting research in women with CPP difficult with the implication that women with CPP may undergo interventions that are not actually required and in studies with relatively small sample sizes, these women pose an increased risk of type I error.
CHAPTER 2: PELVIC VEIN INCOMPETENCE

Introduction

A vascular cause for CPP and its associated symptoms has long been postulated. Pelvic vein incompetence (PVI) was first described by Taylor in 1949. He hypothesised that incompetent and distended pelvic veins caused symptoms of pain secondary to disordered function of the autonomic nervous system after several pregnancies. Similar theories had also been described by Cotte et al who highlighted cases of women with CPP secondary to varices in the broad ligament due to postpartum pelvic thrombophlebitis. The work by Taylor et al was supported by Beard et al in 1984 who demonstrated a causal relationship by showing women with PVI and CPP describing symptom relief after treatment with vaso-constricting drugs.

Nomenclature used to describe ‘pelvic vein incompetence’ is variable and used interchangeably in literature. Frequent terms used include ‘pelvic congestion syndrome’, ‘female pelvic varicocele’, ‘pelvic venous reflux’ and ‘pelvic venous congestion’. PVI is still rarely diagnosed in the UK and often overlooked by gynaecologists as the dilated veins empty during routine laparoscopy when patients are placed head down making them less obvious.

More recently with the advent of improved imaging an association between PVI and CPP is becoming increasingly recognised leading to women undergoing unproven treatments for PVI in the UK and European private sector. Several treatments have been studied for PVI including pelvic vein ligation, coil embolisation, hormonal therapy and even hysterectomy. Current evidence on the effectiveness of these treatments is discussed later in this chapter.
The development of pelvic vein incompetence

Although the explanation of how dilated, refluxing pelvic veins cause pelvic pain symptoms is still unclear, possible causes for the presence of PVI can be broadly classified into anatomical, pregnancy related and hormonal.

Anatomical

Left ovarian vein drainage: The ovaries develop on the posterior abdominal wall at the same level as the mesonephric duct and developing kidneys. Arterial supply and venous drainage is all derived at this level during development. As the ovaries are drawn downwards in the second trimester the arterial supply and venous drainage is maintained.

The left ovarian vein drains directly into the left renal vein at a right angle, whilst the right ovarian vein drains into the inferior vena cava. This anatomical difference is thought to facilitate reflux and proposed as the most likely reason that the left ovarian vein is often the most likely vein to be found to be incompetent, as shown in figure 5. Incompetence in the left ovarian vein can lead to a backpressure along the pelvic plexus and the development of raised venous pressure and incompetence in the right ovarian and internal iliac veins. The angle at which the right ovarian vein enters the inferior vena cava can be between 0-60 degrees which is thought to elicit a valve effect that can again lead to venous hypertension and reflux.
Venous valves: A rich anastomotic venous plexus is responsible for draining the pelvic viscera and includes connections between ovarian, uterine, vulvar, rectal, vesicle, and upper thigh venous systems. Valves in the ovarian vein are thought to be absent in approximately 15% of women, and even when present are thought to be incompetent 43% of the time. This absence of working vein valves is seen as an important factor in the development of PVI. Communications between the pelvic viscera, rectal and upper thigh venous systems is also often valve-less which supports the growing evidence suggesting that PVI precipitates vulval and leg varicose veins and haemorrhoids.
Pregnancy

Growth of the gravid uterus results in profound increases in pelvic blood flow (up to 60 times the pre-gravid volume)\textsuperscript{63} with pelvic vein diameters increasing to the point where valve cusps cannot meet, enabling retrograde flow or the reflux that we call pelvic vein incompetence. Although in many women this incompetence resolves with reduced post-partum blood flow, it seems to persist in up to 25\% of all post-partum women. This effect is exacerbated by the relaxant properties of progesterone, substance P, neurokinins A and B which increase vein dilation.\textsuperscript{64-66} Postpartum there is no chemical or hormonally driven process to reverse this physiological insult onto the venous system.

In addition the weight gain and positional changes of the gravid uterus that occur during pregnancy can cause kinking of the ovarian veins and subsequent venous congestion.

Mechanical compression

In rare cases compression of the left renal vein between the aorta and the superior mesenteric artery (referred to as nutcracker syndrome) can lead to left renal vein venous hypertension and subsequent development of venous varicosities of the renal pelvis and gonadal veins. Compression of the left iliac vein by the overriding right iliac artery (May-turner syndrome) has also been described in the literature typically as case reports.\textsuperscript{67}

Hormone dysfunction

It has been suggested that oestrogen is a venous dilator and that hypo-oestrogenic states or the use of progesterone to antagonize the effects of oestrogen has results in the improvement in CPP symptoms secondary to PVI. Early research also reports symptoms associated with PVI disappearing after menopause suggesting an ovarian-driven process.\textsuperscript{68}
A RCT comparing Medroxy Progesterone (MPA), a synthetic form of progesterone with a placebo in women suspected to have pelvic congestion syndrome (PCS) reported to improve self-reported pain scores after four months of treatment. However these benefits were not seen after nine months of treatment. GnRH (follicle stimulating hormone) agonists were compared with daily MPA in a further trial in women with PVI. After 12 months participants treated with the GnRH agonists had improved pain symptoms, better mood and sexual function. Side effects of both treatments included bloating, weight gain, hot flushes, night sweats and mood changes.

**How pelvic vein incompetence may cause pelvic pain**
Women found to have both PVI and lower limb varicosities are reported to have higher pelvic pain levels when compared with women with isolated lower limb varicose veins. Although venous distension is not thought to cause pain, the stretching and stasis of the dilated and refluxing pelvic veins can lead to the activation of selective pain receptors in the vessel walls, causing a dull pain secondary to the low concentration of nociceptive afferents within viscera.
Prevalence
The frequency of PVI in the general population of women with pelvic symptoms is still unknown. An in-depth literature search identified only five studies that attempted to determine PVI prevalence in a variety of female cohorts.

Study 1: Belenky A, Bartal G, Atar E, Cohen M, Bachar GN. Ovarian varices in healthy female kidney donors: incidence, morbidity, and clinical outcome.72

Over a seven-year period, 273 healthy female kidney donors with a mean age of 43 years were investigated for ovarian vein incompetence using abdominal aortography. In total 27 of 273 (9.9%) were found to have retrograde flow in an incompetent left ovarian vein. The right ovarian and internal iliac veins were not reported on. Interesting nearly half (13 of 27, 48%) of the women reported to have CPP.

Research into reflux patterns has shown that internal iliac vein incompetence is present in nearly 50% of cases and therefore one can assume the minimum prevalence of PVI in women is 10%.73

Study 2: Marsh P, Holdstock J, Harrison C, Smith C, Price BA, Whiteley MS. Pelvic vein reflux in female patients with varicose veins: comparison of incidence between a specialist private vein clinic and the vascular department of a National Health Service District General Hospital.74

The presence of PVI in women with recurrent varicose veins was investigated in an observational study. A total of 462 women with recurrent varicose veins were investigated for non-saphenous reflux using lower limb duplex ultrasound. In total of 90 participants (19.5%) were found to have possible pelvic vein reflux and underwent further imaging using trans-vaginal ultrasound. Of the 90 patients investigated further, 73 (15.8%) were found to have PVI.
**Study 3:** Asciutto G, Asciutto KC, Mumme A, Geier B. Pelvic venous incompetence: reflux patterns and treatment results.\(^{73}\)

100 women with ‘pelvic congestion syndrome’ presenting with vulvar or buttock varices and associated pelvic discomfort were investigated using reflux venography. Mean participant age was 49 ± 11 years. Of the 100 women, 71 (71%) were shown to have PVI. The patient cohort used in this study is very selective and therefore the prevalence of PVI is expected to be high as these women have both varicose veins and pelvic pain; both synonymous with PVI.

**Study 4:** Perrin MR, Labropoulos N, Leon LR, Jr. Presentation of the patient with recurrent varices after surgery (REVAS).\(^{75}\)

170 individuals with recurrent varicose veins were investigated for pelvic reflux using lower limb duplex ultrasound. Mean age was 55.6 ± 12 years. Only 69% of the cohort studied were women. Pelvic vein reflux was identified in 16.7% of patients using only lower limb duplex ultrasound.

**Study 5:** Gultasli NZ, Kurt A, Ipek A, Gumus M, Yazicioglu KR, Dilmen G, et al. The relation between pelvic varicose veins, chronic pelvic pain and lower extremity venous insufficiency in women.\(^{76}\)

This well-designed study evaluated 100 women with CPP of undetermined origin lasting more than six months were investigated using both trans-vaginal Doppler ultrasound and lower limb Doppler ultrasound. PVI was identified in 30 of 100 (30%) women. In total, 21 of 30 (70%) also had associated lower limb venous insufficiency.

Based on the available evidence, one can assume that PVI prevalence in a female population is between 10-15%. The frequency of PVI in women with CPP can be estimated to be around 20-30%.
Clinical features

The clinical presentation of women with PVI is largely based on evidence from case series, expert opinions and published reports. Presentation of women with PVI can be broadly categorised into pelvic pain symptoms, varicose veins and a select few associated features.

Pelvic pain symptoms

The most commonly described symptom thought to be experienced by women with PVI is pelvic or lower abdominal pain.\textsuperscript{64,68} Although it is rare for studies or case series to elaborate further on the nature of the pain; it is described as a unilateral, dull heaviness in several published reports.\textsuperscript{70} This pain was often found to be exacerbated by prolonged standing and pregnancy.\textsuperscript{60,64,66,77} Painful sexual intercourse and symptoms exacerbated by menstruation or pregnancy has also been reported to be associated with PVI or pelvic congestion syndrome.\textsuperscript{56} In reality, it would be difficult to exclude common differential diagnosis such as endometriosis or pelvic inflammatory disease based on pelvic pain history alone.

Varicose veins

Primary varicose veins usually involve the long saphenous (75%) or the short saphenous (20%) system with occasional perforating veins.\textsuperscript{78} Varicose veins due to PVI do not conform to this usual patterns but instead are seen to arise from the pelvis and are typically located in the upper medial thigh (vulvar) or posterior thigh and buttock areas (figure 6 and 7).\textsuperscript{79,80,81} Vulvar varices seen in pregnancy typically regress on delivery.\textsuperscript{82}

Recurrence of varicose veins after treatment is common with accepted causes including inadequate intervention, misdiagnosis and neovascularisation after surgery.\textsuperscript{76} Recurrence due to PVI is thought to affect over 30% of women and is often overlooked.\textsuperscript{83} Studies have shown significant agreement between lower limb
ultrasonography findings and trans-vaginal findings. Recent guidelines suggested the treatment of PVI before attempting to manage lower limb varicosities.

Figure 6 Varicose veins filling from the sapheno-femoral junction (a), and vulvar varices filling from pelvic vein incompetence (b)

Figure 7 Peri-vulvar varices extending over the buttocks and across the posterior thigh
**Associated features**

Several conditions or symptoms have been reported to be associated with PVI and CPP. This includes systemic features such as headaches, fatigue, bloating, leg aches, low mood and nausea.\(^88\)\(^70\)

Haemorrhoids are vascular ano-rectal structures that contribute to the drainage of the anal canal and help maintain continence that have been linked with PVI.\(^89\)\(^90\) Haemorrhoids can become enlarged and symptomatic secondary to chronic constipation, straining during defecation, and increased intra-abdominal pressure.\(^91\) The association between haemorrhoids and PVI was first highlighted in 2012 when it was reported that treatment of PVI by trans-venous occlusion eliminated haemorrhoids.\(^92\) In a further study, 153 women with PVI were examined. Of these 153 women, 56 (36.3\%) were found to have haemorrhoids. When examining the pattern of reflux demonstrated on trans-vaginal Doppler ultrasound the incompetence would often occur in the internal iliac veins with none of the 56 patients in this group demonstrating reflux of the ovarian veins in isolation.\(^93\) Figures 8 and 9 demonstrate haemorrhoids and perianal veins seen on trans-vaginal ultrasound.\(^93\)
Figure 8 Trans-vaginal ultrasound scan view of haemorrhoids and perianal veins

Figure 9 TVU view of a right internal iliac vein feeding into haemorrhoids
Diagnosis

Several methods of identifying and diagnosing PVI have been evaluated. This includes abdominal and trans-vaginal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and reflux venography which is commonly accepted as the reference standard. Reports of accuracy of diagnosing PVI is often dependent on the definitions used to define the condition of which there is no clear consensus of.

Pelvic ultrasound

Ultrasound uses sound waves of varying frequencies to generate images. Pelvic Doppler ultrasound utilised via the trans-vaginal or trans-abdominal approach is relatively cheap to perform and safe, avoiding exposure to radiation or contrast to radiosensitive ovaries. Trans-vaginal ultrasound (TVU) allows better visualisation of pelvic organs and vessels for more accurate assessment of pelvic vessel diameter and direction of flow (figures 10 and 11).
Figure 10 TVU in a woman in the semi-standing position with Valsalva

Figure 11 TVU in a woman in the semi-standing position with thigh compression and release
The most effective method of generating reflux during TVU is still unclear. The use of the semi-standing position with and without Valsalva uses gravity to test valve competence and improve sonographic assessment and is evaluated further in chapter 5.

Four studies evaluated TVU capabilities in measuring pelvic vein diameter and flow direction. Two studies used a ‘congestion score’ which included assessment of vein diameter, number of varices, and a subjective congestion assessment (absent, moderate or severe).

A weak positive correlation between individual TVU and venography congestion scores (r=0.29; p=0.06) was seen in one study.94 TVU performed in the supine position only with no Valsalva was reported to be unable to discriminate women with confirmed PVI with healthy controls in one study with no significant difference reported in diameter or number of veins visible.95 However Giacchetto et al reported that TVU in the supine position was effective at differentiating women with PVI from controls, and reported women with PVI to have a greater mean left ovarian diameter than women without PVI (10.7mm versus 3.6mm, p<0.001). When compared with trans-abdominal ultrasound, TVU was only able to identify 7 of 32 women with confirmed PVI on venography.96

**Reflux venography**

Performed immediately before embolisation, catheter directed venography is the considered the reference standard method of diagnosing PVI.97 Iodinated contrast is injected via the catheter with the patient in a semi-erect position during the Valsalva manoeuvre, allowing for assessment of both venous distension and reflux.59 It is thought to be most effective and widely applicable technique for visualising incompetent pelvic veins but involves exposing young women to radiation and nephrotoxic contrast. Reflux can be shown by Valsalva manoeuvre or by tilting the patient feet down allowing the veins to fill (figure 12 and 13).73

Reflux venography was first studied by Beard et al in 1984. In his study, trans-uterine venography was performed in 45 women with CPP and a normal
laparoscopy. Eight of these women were healthy controls attending hospital for sterilisation. Ten women were diagnosed with other pathology before inclusion into this study (endometriosis (4), pelvic inflammatory disease (4) and adhesions (2)).

The primary outcome measure was a venogram score consisting of: diameter of ovarian veins, timing of dye disappearance, and congestion appearance. The authors reported that mean diameter of ovarian veins in women with PVI was 6.73 +/- 3.14 mm compared with 3.6 +/- 1.76 mm in women with confirmed pathology and 3.25 +/- 2.38 mm in women with no CPP symptoms (p<0.01). Since then it has been studies in relatively small clinical trials with no consensus on diagnostic criteria or technical protocol. Comparison between TVU and reflux venography was associated with a 96.2% sensitivity and 100% specificity.

Figure 12 Reflux venography showing reflux in the left ovarian vein
Computed tomographic (CT) and magnetic resonance imaging (MRI)

CT and MRI are both non-invasive imaging techniques which allow a complete examination of the pelvic anatomy with multi-planar imaging as shown in figure 14. Both modalities can identify ovarian varices and provide information of co-existing pathology. MRI has the added advantage that it can avoid radiation, but cannot be used to follow up patients after coil embolisation due to metallic artefact. CT involves the use of a contrast agent and radiation. Both MRI and CT are conventionally performed with the patient in supine position, which can lead to under filled varices.59
Five studies assessed the role of CT or MRI for the diagnosis of pelvic vein incompetence. Phase-contrast velocity mapping (PCVM) was found to be effective at identifying incompetent veins after direct venography in women with clinical PVI. PCVM also showed competent ovarian veins to have a homogenous (laminar) flow pattern whereas incompetent ovarian veins showed a turbulent flow pattern throughout the cardiac cycle. The sensitivity and specificity of MR venography in detecting PVI was found to be 88%, 100% and 91% in the ovarian, internal iliac and pelvic plexus respectively with specificity of 67%, 38% and 42% respectively.

Helical CT scans of 34 healthy asymptomatic consecutive female kidney donors aged between 18-46 years were evaluated in one study. PVI was found in 16 of the 34 (47%) asymptomatic women. All 16 had left ovarian vein involvement, and 6 of 34 (37.5%) had bilateral ovarian vein involvement.

All studies failed to meet many key criteria of the STARD guidelines (encompassing explicit study classification, participant selection, proper reference standard,
rational and reproducible test methodology, rigorous statistical methodology, complete reporting of results, and precision of reported estimates).

The poor design of these studies precludes any meaningful attempt to systemically critique these by modality. All the studies reported that vein diameter was greater in women with PVI but the studies did not agree on cutoffs or use validated measures for congestion/tortuosity.

**Treatment**

Several treatments have been suggested for PVI. These include pelvic vein ligation or occlusion, hormonal therapy and even hysterectomy. All the studies reviewed as part of this thesis were of poor study design and classified as low grade evidence. Outcome measures used in the studies were heterogeneous making summary estimates of treatment effect difficult. Only three RCTs were identified.

**Trans-venous occlusion**

Trans-venous occlusion is performed under local anaesthesia. The catheter is introduced through the right jugular vein and incompetence where present will be confirmed by reflux venography. Incompetent veins are treated with either i) a distal and proximal occluding coil with foam sclerotherapy sandwiched in between, ii) several metallic coils or iii) foam sclerotherapy only (figure 15). Patients can go home 1-2 hours following the procedure and usually do not require analgesia. Thirteen studies evaluating trans-venous occlusion as a form of treatment for pelvic vein incompetence were identified and are discussed in detail in chapter 8.
Figure 15 Left ovarian incompetence (a) will filling pelvic varices in (b). The insertion of coils first into the pelvic varices (d) and then the ovarian vein (c) shows the prevention of reflux.
**Hormonal therapy**

Five studies assessed ovarian suppression therapy as a form of treatment for PVI encompassing 215 women. This included three randomised control trials. The rationale for the use of hormonal therapy for PVI is still unclear, but the daily administration of Medroxy-progesterone (MPA) resulted in significant reduction in pelvic congestion compared with placebo (73% vs. 33%, n=104; p<0.001) which was only sustained up to nine months.\(^6^9\) In a second RCT, MPA was compared with GnRH agonist Goserelin; women being treated with Goserlin after one year showed greater improvements in pain, sexual function and depressive symptoms 12 months after completion of treatment.\(^6^8\)

Side effects from hormonal therapy include bloating, weight gain, hot flushes, night sweats, vaginal dryness and mood changes.\(^6^9\)

**Surgery**

Surgical treatment in the form of surgical ligation and hysterectomy (with and without salpingo-oophorectomy) was assessed in four studies on 128 women with CPP thought to be caused by PVI. All four trials were of retrospective design with small sample sizes potentially making them subject to type II error.

Surgical ligation of the left ovarian vein was assessed in two studies encompassing 38 women and showed that over 53% of women were completely pain free after ligation, with a further 20% describing considerable improvement.\(^1^0^3\)\(^ \, \, ^1^0^4\)

Hysterectomy with and without salpingectomy was assessed in two studies, of which one was a quasi-randomised trial.\(^1^0^5\)\(^ \, \, ^1^0^6\) This study compared coil embolisation with hysterectomy plus bilateral oophorectomy, and hysterectomy plus unilateral oophorectomy in 106 women; there was no control group receiving no treatment. Trans-venous occlusion by coil embolisation was significantly more effective at reducing pelvic pain than hysterectomy with uni- or bilateral oophorectomy (p<0.05). However this study failed to describe its randomisation process, and there was no attempt to ‘blind’ the outcome assessment, leaving the
study at a risk of bias. Follow up and analysis was adequate, but loss to follow up data was not reported, which may represent selective reporting.\textsuperscript{105}

\textbf{Current practices}
A survey of current practices and awareness of PVI amongst clinicians was conducted as part of a recent NIHR-funded review. Although the response rate was poor (6\%) it demonstrated that most clinicians would consider the diagnosis of PVI if a patient presents with dull pain exacerbated by standing, dyspareunia and dilated ovarian veins on imaging. Their survey found that TVU and laparoscopy were the commonest diagnostic imaging modalities use by clinicians investigating PVI. Only one out of 18 clinicians reported that they frequently use MRI instead. The survey showed that the frequency of diagnosis of PVI was variable with some clinicians describing it as a coincidental finding and others suggesting it to be under diagnosed. The overwhelming majority of Interventional Radiologists involved in the treatment of PVI stated that there was a great need for evidence base regarding its treatment to be strengthened by data from a RCT.
**Chapter summary**

PVI has been implicated as a cause for CPP since the 1940s, however this association has never been illustrated in well-designed clinical studies. The nature of the pain and discomfort experienced with PVI is suggested to be similar to that experienced by women with CPP syndrome with a few distinctive features; namely pain which worsens on prolonged standing and the association with varicose veins of the leg and vulvar region. The current reference standard investigation is an invasive procedure which exposes young women to radiation and nephrotoxic contrast. Alternatives such as trans-vaginal Doppler ultrasound are increasingly used but have not been studied in well-designed clinical trials. The safest and most effective treatment for PVI and whether it actually improves symptoms of CPP is still unknown. Research conducted to date has been predominately retrospective cohort studies with only a handful of small randomised prospective trials. Trans-venous occlusion in theory provides a safer alternative to surgery with a better side effect profile when compared to hormonal therapy. However it is yet to be evaluated in a well-designed clinical trial.
CHAPTER 3: THESIS OBJECTIVES AND METHODS

This thesis aims to advance our understanding of PVI and further elucidate its role in chronic pelvic pain. The research questions that this thesis aims to answer and the methods used are described in brief below. A more detailed explanation of the methods is documented in each individual chapter. In line with the alternative format, each individual chapter is presented as a journal manuscript with a discussion chapter following these.

Research Questions 1-3

1. Do women with pelvic vein incompetence experience symptoms that are not seen in matched women with typical varicose veins, or in healthy women?

2. Do women with pelvic vein incompetence have a reduced health-related quality of life as assessed by the Euroqol health score (EQ-5D-3 Level)?

3. Do women with pelvic vein incompetence use more healthcare resources and incur more NHS costs then matched women with typical varicose veins, or healthy women?

Methods

A case-control study comparing 40 women with confirmed PVI on trans-vaginal ultrasound with 40 matched women with varicose veins of the leg only and 40 matched healthy controls with no PVI or varicose veins was conducted. All participants were asked to complete a health questionnaire designed for this study to collect information on each participant’s demographics, gynaecological and pain history. The Euroqol 3-level score was used to determine health-related quality of life. Participants were also asked to comment on their use of over the counter medication, number of visits to health professionals and the requirement for admission to manage pelvic pain symptoms.
Research Questions 4-6

4. What is the most effective method of demonstrating pelvic vein incompetence when using trans-vaginal Doppler ultrasound?

5. Can trans-vaginal ultrasound detect pelvic vein incompetence with accuracy compared with the current reference standard reflux venography?

6. Do women find Doppler trans-vaginal ultrasound scan to be an acceptable investigation for chronic pelvic pain?

Methods

Fifty women undergoing trans-vaginal ultrasound to detect PVI were consented to undergo a variety of positions and manoeuvres to determine the most effective method of detecting PVI. Participants were assessed in the supine and semi-standing positions with the addition of Valsalva manoeuvre and thigh compression and release. The effect each position (+/- provocative) had on vein diameter and reflux time was assessed. Inter-observer variability and readability were also determined. Women undergoing the scan were asked to complete a short questionnaire on the acceptability of the investigation. They were asked to comment on comfort and how it compared with previous scans they may have had in the past.

Twenty-two women who had undergone trans-vaginal ultrasound then went on to have reflux venography and trans-venous occlusion of their PVI. The 44-paired scans were compared to determine overall accuracy.

Research Question 7

7. Are women of reproductive age suffering from chronic pelvic pain more likely to have PVI than age and parity matched women without chronic pelvic pain?
Methods
A case-control study comparing 35 women with chronic pelvic pain (with a normal laparoscopy) diagnosed by a gynaecologist with 35 healthy women (no history of chronic pelvic pain) was conducted. All cases were aged 18-49 years and matched with to a healthy control. All participants underwent a trans-vaginal ultrasound scan to determine the presence of PVI. The prevalence, description of pain symptoms and quality of life were compared.

Research Questions 8-9
8. What is the evidence underpinning the use of trans-venous occlusion of pelvic veins as a treatment for chronic pelvic pain?

9. Is trans-venous occlusion of pelvic veins an effective treatment for chronic pelvic pain?

Methods
A systematic review of clinical studies investigating the use of foam or coil occlusion of pelvic veins for chronic pelvic pain was conducted. Each study was critically appraised and its quality assessed using the Critical Appraisal Skills Programme (CASP) tool.

A randomized-control trial protocol investigating the impact of trans-venous occlusion as a treatment for PVI was designed and submitted for external funding to the National Institute of Health Research (NIHR). It was approved for funding and started in September 2015.
Abstract

**Background:** Pelvic vein incompetence (PVI) affects 15-20% of all women, yet we know little about how it affects sufferers. The aim of this prospective study was to explore symptoms experienced by women with PVI, and determine its impact on quality of life and NHS costs.

**Methods:** Cases were 40 premenopausal women aged 18-49 years with PVI and varicose veins (VV). There were two age-matched controls groups: i) 40 healthy women with no PVI but with VV, and ii) 40 healthy women with no PVI and no VV. Subjects were asked to complete a structured questionnaire on disease specific outcomes, health status and use of healthcare resources.

**Results:** Mean age (range) was 39.8 (24-47) years for cases, 39.1 (24-49) for VV controls and 38 (25-49) for healthy controls. Pelvic pain was reported by 38 of 40 (95%) PVI cases, compared with 25 of 40 (62%) VV controls, and 26 of 40 (65%) healthy controls (p=0.001). The median (range) EQ-5D utility score for PVI cases was 0.80 (0.29-1.0) compared with 0.80 (0.09-1.0) for VV controls and 1.0 (0.62-1.0) for healthy controls (p=0.002). Of the 40 PVI cases, 35 (88%) visited a consultant in the previous 12 months compared with 12 of 40 (30%) VV controls, and 14 of 40 (35%) healthy controls (p<0.001).

**Conclusions:** Women with PVI report a greater frequency of pelvic pain with reduced health status and increased use of healthcare resources compared with matched controls.
Introduction

Chronic pelvic pain (CPP) affects 24% of women worldwide and accounts for 20-40% of all gynaecology outpatient appointments in the UK. CPP primarily affects younger women and is a leading cause of reduced quality of life with physical, psychological and emotional upset. Many women never achieve a diagnosis and are often subjected to repeated hospital admissions and invasive investigations such as laparoscopy. Some are even offered hysterectomy which is frequently unsuccessful.

Pelvic vein incompetence (PVI), first described by Taylor in 1949 is thought to be a cause of pelvic pain, dyspareunia and menstrual dysfunction. It affects 15-20% of women but is still poorly understood and the epidemiology and optimal diagnostic approach is poorly studied. There is no guidance on the management of PVI from the Royal College of Obstetrics and Gynaecology (RCOG) or the National Institute of Care Excellence (NICE). The equivalent condition in men, varicoceles caused by testicular vein incompetence, is treated on the NHS whereas most women suffering from PVI in the UK cannot access NHS treatment.

The aim of this prospective characterisation study was to explore the symptoms experienced by women with PVI, its impact on quality of life and their use of healthcare resources.
Methods

Participants and settings

Forty premenopausal women aged 18-49 years with varicose veins (VV) and PVI confirmed on trans-vaginal ultrasound (TVU) were recruited over an eight-month period from the vascular clinic at a UK University Hospital. The indication to investigate women for PVI by TVU was atypical vulval or posterior thigh VVs, or evidence of refluxing veins originating from the pelvis on lower limb duplex ultrasound.

Two groups of controls were individually matched for age within two years to each case; i) women with VV with no clinical signs of PVI recruited from a VV clinic (40 VV controls) and ii) healthy women with no VV or PVI from the open access ENT clinic (40 healthy controls).

Exclusion criteria were i) post-menopausal ii) pregnant or within 12 months of pregnancy iii) history of venous thromboembolism, ischaemic heart disease or stroke iv) history of heart, renal or liver failure v) any diagnosis or treatment for malignancy within 12 months vi) hysterectomy vii) body mass index (BMI) >40 or viii) unable to give informed consent.

Local ethics committee approval was obtained (reference 12/NW/0761). All potential participants were provided with study information leaflets and written consent was obtained. Our patient and public involvement (PPI) group, consisting of four women with PVI and five women with CPP, provided guidance on study design, recruitment and the development of patient materials such as the information leaflet and consent forms.
Trans-vaginal ultrasound

All TVU investigations were performed in both supine and semi-standing positions by the same experienced vascular scientist. The internal iliac and ovarian veins on each side were isolated, the diameter measured (mm) and the presence of dilated or tortuous veins around the ovaries and uterus were recorded. PVI was defined as sustained reflux > 0.5 seconds generated by Valsalva or thigh compression and release.

Reflux venography is regarded as the ‘gold standard’ diagnostic tool for pelvic vein incompetence; however it is an invasive procedure involving jugular vein puncture, contrast and radiation. TVU is becoming an accepted alternative to reflux venography.64 74

Symptoms and quality of life score

All participants were asked to complete a structured questionnaire on symptoms, health related quality of life and use of healthcare resources.

Despite a diligent search, we failed to identify a single existing questionnaire or disease specific outcome measure which adequately captured issues relevant to both PVI and CPP. Under the guidance of our PPI group, a health questionnaire was designed by extracting validated questions from several well-known outcome measures. Although not validated, this customised health questionnaire served to collect information regarding pain symptoms and their broader impact on subjects. Questions used in the customised health questionnaire were selected from the following validated scores: i) International Pelvic Pain Society assessment form, 28 ii) the Endometriosis Health Profile (EHP-30), 109 iii) the British Society of Gynaecological Endoscopy (BSGE) pelvic pain questionnaire, 110 iv) the heavy menstrual bleeding national audit questionnaire, 111 and v) the VEINES symptom questionnaire. 112 The health questionnaire also included visual analogue scores (VAS) to measure the severity of pain. It was piloted by our PPI group members who reported that it was easy to understand and relevant.
Current health status was assessed using EuroQol (EQ-5D-3L). The EQ-5D-3L system is a generic, multi-attribute, preference-based measure made up of five three-level domains: mobility, pain/discomfort, self-care, usual activities, and anxiety. Use of healthcare resources (e.g. visits to healthcare professionals, in-patient or Accident and Emergency visits) and out-of-pocket costs (e.g. over the counter medicine) over the previous 12 months was also reported with the clinic visit that triggered recruitment excluded.

**Statistical analysis**

Since this study conducted to inform future power calculations for research in PVI, no formal power calculation was performed. The sample size of 40 subjects per group was chosen as this would be sufficient to detect a 30% difference in the frequency of pelvic pain between groups at the conventional 5% statistical significance.

Statistical analysis was conducted using SPSS® versions 20 (SPSS®, Chicago, USA). Categorical data was analysed using chi-squared test and continuous data with ANOVA, followed by Scheffe’s tests or Kruskal-Wallis tests with Bonferroni-adjusted Mann-Whitney U-tests as appropriate. For the non-normally distributed VAS severity scores, additional group comparisons were made on the restricted cohort with parity greater than zero. The conventional 5% significance level was used.

Published UK social preference weightings were used to transform EQ-5D-3L scores into a measure of health-related quality of life (HR-QoL). Use of healthcare resources by women with PVI (cases) was compared with the VV and healthy control women separately. Unit costs derived from the Personal Social Services Research Unit 2012 were attached to healthcare resources and descriptive statistics were used to summarise the direct healthcare costs in the cases and control groups.
Results

Forty cases with confirmed PVI on TVU were recruited from the vascular surgery clinic at a tertiary vascular centre. Forty women with leg VV only were recruited from the varicose vein clinic based at the same hospital. Forty healthy women were recruited from the open access ENT clinic.

Comparability of groups

Mean age (range) was 39.8 (24-47) for the PVI cases, 39.1 (24-50) for VV controls and 38 (25-49) for healthy controls (ANOVA; Scheffes test). PVI cases had significantly higher median (range) gravida of 2.5 (0-8), compared with 1.5 (0-10) in VV controls and 2 (0-6) in healthy women (p=0.047). Median parity was also significantly higher in PVI cases (p=0.007, Kruskal-Wallis; Bonferonni-corrected Mann-Whitney tests). BMI was marginally but significantly lower in PVI cases at 24 (19-31) compared with 26 (17-42) and 26 (20-37) in VV controls and healthy controls respectively (p=0.017). Smoking history was similar in the three groups (p=0.26, chi-square test).
Table 2 Cases and matched control comparability

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=40)</th>
<th>VV controls (n=40)</th>
<th>Healthy women (n=40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>39.8 (24-47)</td>
<td>39.1 (24-50)</td>
<td>38 (25-49)</td>
<td></td>
</tr>
<tr>
<td>Median gravida</td>
<td>2.5 (0-8)</td>
<td>1.5 (0-10)</td>
<td>2 (0-6)</td>
<td>p=0.047*</td>
</tr>
<tr>
<td>Median parity</td>
<td>2 (0-5)</td>
<td>1 (0-5)</td>
<td>1 (0-5)</td>
<td>p=0.007*</td>
</tr>
<tr>
<td>Mean BMI</td>
<td>24 (19-31)</td>
<td>26 (17-42)</td>
<td>26 (20-37)</td>
<td>p=0.017#</td>
</tr>
<tr>
<td>Smoking (n,%)</td>
<td>6 (15%)</td>
<td>3 (8%)</td>
<td>10 (25%)</td>
<td>p=0.26*</td>
</tr>
</tbody>
</table>

* Chi-squared tests; * two sampled t-test

Symptom history

Pelvic pain was reported by 38 of 40 (95%) PVI cases, compared with 25 of 40 (62%) VV controls and 26 of 40 (65%) healthy controls (p<0.001) (table 3). This pain in PVI cases was found to occur throughout the month (p<0.001), before and during periods (p=0.001), and during sexual intercourse (p=0.007). Severity was assessed using VAS. Median recorded VAS was significantly higher in PVI cases in pain experienced throughout the month and before or during the menstrual cycle (p<0.001) (table 4). Women with PVI described the pain as dull in nature and worse on prolonged standing or walking; it radiated into the upper thighs in 16 of 38 (42%) PVI cases with pelvic pain, compared with only 2 of 25 (8%) VV controls with pain, and 3 of 26 (12%) healthy controls with pain (p<0.001).
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cases (n=40)</th>
<th>VV controls (n=40)</th>
<th>Healthy women (n=40)</th>
<th>Comparison over 3 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic Pain</td>
<td>38 (95%)</td>
<td>25 (62%)</td>
<td>26 (65%)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>95%</td>
<td>62%</td>
<td>67%</td>
<td>P=0.008</td>
</tr>
<tr>
<td>Pain before periods</td>
<td>33 (82%)</td>
<td>17 (42%)</td>
<td>20 (50%)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>83%</td>
<td>42%</td>
<td>51%</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Pain during periods</td>
<td>38 (95%)</td>
<td>24 (60%)</td>
<td>26 (65%)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>95%</td>
<td>59%</td>
<td>67%</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Pain throughout month</td>
<td>28 (70%)</td>
<td>10 (25%)</td>
<td>7 (18%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>74%</td>
<td>22%</td>
<td>16%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Pain during sexual intercourse</td>
<td>17 (42%)</td>
<td>7 (18%)</td>
<td>6 (15%)</td>
<td>P=0.007</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>42%</td>
<td>18%</td>
<td>16%</td>
<td>P=0.023</td>
</tr>
<tr>
<td>Pain opening bowels</td>
<td>8 (20%)</td>
<td>5 (12%)</td>
<td>3 (8%)</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>19%</td>
<td>13%</td>
<td>8%</td>
<td>P=0.36</td>
</tr>
<tr>
<td>Lower back pain</td>
<td>28 (70%)</td>
<td>21 (52%)</td>
<td>23 (58%)</td>
<td>P=0.26</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>71%</td>
<td>52%</td>
<td>58%</td>
<td>P=0.22</td>
</tr>
<tr>
<td>Feeling bloated</td>
<td>28 (70%)</td>
<td>22 (55%)</td>
<td>21 (52%)</td>
<td>P=0.23</td>
</tr>
<tr>
<td>Adjusted % *</td>
<td>71%</td>
<td>54%</td>
<td>52%</td>
<td>P=0.23</td>
</tr>
</tbody>
</table>

* adjusted for parity and BMI; Overall chi-square test and chi-square tests with Bonferroni correction
<table>
<thead>
<tr>
<th></th>
<th>Median (range)</th>
<th>Cases (n=40)</th>
<th>VV controls (n=40)</th>
<th>Healthy women (n=40)</th>
<th>Comparison over 3 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain before periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 (0, 75)</td>
<td>0 (0, 75)</td>
<td>12 (0,75)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>restricted *</td>
<td></td>
<td>25 (0, 75)</td>
<td>0 (0,50)</td>
<td>0 (0,50)</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Pain during periods</td>
<td></td>
<td>50 (0, 100)</td>
<td>25 (0,75)</td>
<td>25 (0,75)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>restricted *</td>
<td></td>
<td>50 (0, 100)</td>
<td>25 (0,75)</td>
<td>25 (0,50)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Pain throughout month</td>
<td></td>
<td>25 (0, 75)</td>
<td>0 (0,50)</td>
<td>0 (0,38)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>restricted *</td>
<td></td>
<td>25 (0, 75)</td>
<td>0 (0,50)</td>
<td>0 (0,38)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Pain during sexual intercourse</td>
<td></td>
<td>0 (0, 81)</td>
<td>0 (0,75)</td>
<td>0 (0,40)</td>
<td>P=0.018</td>
</tr>
<tr>
<td>restricted *</td>
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<td>0 (0, 81)</td>
<td>0 (0,50)</td>
<td>0 (0,25)</td>
<td>P=0.012</td>
</tr>
<tr>
<td>Pain opening bowels</td>
<td></td>
<td>0 (0,25)</td>
<td>0 (0,25)</td>
<td>0 (0,50)</td>
<td>P=0.29</td>
</tr>
<tr>
<td>restricted *</td>
<td></td>
<td>0 (0,25)</td>
<td>0 (0,25)</td>
<td>0 (0,50)</td>
<td>P=0.42</td>
</tr>
<tr>
<td>Lower back pain</td>
<td></td>
<td>25 (0,88)</td>
<td>25 (0,89)</td>
<td>25 (0,75)</td>
<td>P=0.10</td>
</tr>
<tr>
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<td></td>
<td>25 (0,88)</td>
<td>12 (0,75)</td>
<td>25 (0,75)</td>
<td>P=0.11</td>
</tr>
<tr>
<td>Feeling bloated</td>
<td></td>
<td>25 (0,100)</td>
<td>20 (0,75)</td>
<td>19 (0,75)</td>
<td>P=0.17</td>
</tr>
<tr>
<td>restricted *</td>
<td></td>
<td>25 (0,100)</td>
<td>19 (0,75)</td>
<td>25 (0,75)</td>
<td>P=0.29</td>
</tr>
</tbody>
</table>

Overall chi-square test and chi-square tests with Bonferroni correction

* restricted to those with parity > 0 [Cases n=37, VV controls n=28, Healthy women n=27]  
Kruskal-Wallis and Bonferonni-corrected Mann-Whitney test
Previous varicose vein surgery and reoccurrence

Eighteen of 40 (45%) women with PVI had undergone previous VV surgery compared with 13 of 40 (32%) VV controls. Leg VV’s recurred more quickly in women with PVI, with seven of 18 (41%) reporting recurrence of their VV’s at 12 months after surgery, compared with 1 of 13 (11%) in VV controls (p=0.001). No difference in leg symptoms or discomfort severity was seen between the two groups.

Health status

The median (range) EQ-5D-3L utility score for general health of PVI cases was 0.80 (0.29-1.8) compared with 0.80 (0.09-1.0) for VV controls and 1.0 (0.62-1.0) for healthy controls (p=0.002, Kruskal-Wallis test). Pain/discomfort was the primary limiting factor in quality of life for the PVI and VV patients with no important differences in mobility, self-care, usual activities or anxiety using overall chi-squared test.

Healthcare costs

All participants reported their total use of all healthcare resources over the previous 12 months; these were not limited to the diagnosis and treatment of pelvic pain symptoms. Of the 40 PVI cases, 35 (88%) visited a consultant in the previous 12 months compared with 10 of 40 (25%) VV controls and 14 of 40 (35%) healthy controls (p<0.001) (table 5). Of the 35 PVI patients who visited a consultant, 32 (94%) had seen a consultant more than once. Mean (sd) individual patient costs for outpatient visits were £294.15 ± 206 for PVI cases, £55.65 ± 116 for VV controls and £95.4 ± 175 for healthy controls. The number of GP consultations was not significantly different between the three groups.

The most frequent outcome following outpatient consultation for PVI cases was a request for further investigation, which occurred in 10 of the 35 (29%) PVI women who attending hospital outpatient clinics. Four PVI cases were admitted for
investigation of gynaecological symptoms in the 12-month period (three were offered surgery) compared with one VV control and two healthy controls. Total costs for hospital admissions (based on NHS Reference Costs 2012) was £6732 for the PVI cases, compared with £1683 for VV controls and £3366 for healthy controls.

Twenty-four (60%) PVI cases purchased over the counter (OTC) analgesia during the last 12 months compared with 18 of 40 (45%) VV controls and 15 of 40 (38%) healthy controls.
Table 5 Recorded resource use and cost for the three patient groups (not specifically related to pelvic symptoms)

<table>
<thead>
<tr>
<th>Healthcare consultations</th>
<th>Cases (n=40)</th>
<th>VV controls (n=40)</th>
<th>Healthy controls (n=40)</th>
<th>P-value #</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>39 (98%)</td>
<td>37 (93%)</td>
<td>38 (95%)</td>
<td>0.591</td>
</tr>
<tr>
<td>Practice Nurse</td>
<td>6 (15%)</td>
<td>10 (25%)</td>
<td>14 (35%)</td>
<td>0.118</td>
</tr>
<tr>
<td>Pharmacist</td>
<td>4 (10%)</td>
<td>7 (18%)</td>
<td>6 (15%)</td>
<td>0.222</td>
</tr>
<tr>
<td>Specialist Nurse</td>
<td>4 (10%)</td>
<td>3 (8%)</td>
<td>1 (3%)</td>
<td>0.392</td>
</tr>
<tr>
<td>Consultant</td>
<td>35 (88%)</td>
<td>10 (25%)</td>
<td>14 (35%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GP appointments</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (3%)</td>
<td>3 (8%)</td>
<td>2 (5%)</td>
<td>0.591</td>
</tr>
<tr>
<td>1-2</td>
<td>12 (30%)</td>
<td>13 (33%)</td>
<td>11 (28%)</td>
<td>0.888</td>
</tr>
<tr>
<td>3-4</td>
<td>19 (48%)</td>
<td>16 (40%)</td>
<td>18 (45%)</td>
<td>0.879</td>
</tr>
<tr>
<td>5-6</td>
<td>5 (13%)</td>
<td>4 (10%)</td>
<td>5 (13%)</td>
<td>0.323</td>
</tr>
<tr>
<td>&gt;6</td>
<td>2 (5%)</td>
<td>4 (10%)</td>
<td>4 (10%)</td>
<td>0.431</td>
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</table>

<table>
<thead>
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<th>Outpatient appointments</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>5 (13%)</td>
<td>30 (75%)</td>
<td>26 (65%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1-2</td>
<td>18 (45%)</td>
<td>8 (20%)</td>
<td>10 (25%)</td>
<td>0.361</td>
</tr>
<tr>
<td>3-4</td>
<td>15 (38%)</td>
<td>2 (5%)</td>
<td>3 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5-6</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (3%)</td>
<td>0.601</td>
</tr>
<tr>
<td>&gt;6</td>
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<th>Admission for pelvic pain</th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4 (10%)</td>
<td>1 (3%)</td>
<td>2 (5%)</td>
<td>0.346</td>
</tr>
<tr>
<td>No</td>
<td>36 (90%)</td>
<td>39 (97%)</td>
<td>38 (95%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operation for pelvic pain</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>4 (10%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0.206</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs (E)*</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GP visits (cost per patient)</td>
<td>99.51 ± 55</td>
<td>95.21 ± 61</td>
<td>103.37 ± 59</td>
<td>0.797</td>
</tr>
<tr>
<td>Outpatients (cost per patient)</td>
<td>294.15 ± 206</td>
<td>55.65 ± 116</td>
<td>95.4 ± 175</td>
<td>0.256</td>
</tr>
<tr>
<td>Inpatients (total cost per group)</td>
<td>6732</td>
<td>1683</td>
<td>3366</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mean ± (SD) costs taken from NHS Reference Costs 2012
# Chi-squared tests
Discussion

Women with PVI experience more lower abdominal and pelvic pain than age-matched women with VV or healthy controls. They are greater users of healthcare resources, and have an impaired quality of life compared with healthy women.

The strength of this study is inclusion of well-matched controls. All subjects were hospital attendees matched for age, and statistical analysis was adjusted for parity and BMI. PVI was diagnosed using TVU which is widely accepted as a safe, objective and minimally invasive method of diagnosing PVI. Reflux venography, although essential as part of treatment, exposes women to ionising radiation, nephrotoxic contrast and the risks of jugular vein puncture and would not have been appropriate in a study recruiting control subjects.

The health questionnaire used in this study was designed by the research team using previously validated questions to collect information from subjects. This format allowed us to collect a wide range of information from our subjects using questions that had been shown to be useful and reliable in previous studies. No attempt was made to define pelvic pain in our study as our PPI group felt this may bias the reporting of the types of pain and symptoms experienced by our subjects. The consequences of this broad use of terms was that women with VVs and healthy women controls reported a higher frequency of pelvic pain than would be expected.

We know very little about PVI even though it is thought to affect 15-20% of all women. The relationship between PVI and CPP has never been formally explored in an adequately designed epidemiological study. Published reports on women with PVI suggest that they suffer from dull unilateral pelvic pain with associated dysmenorrhoea and dyspareunia. Other reported symptoms include vulvar swelling, leg fullness, persistent genital arousal and lower backache. There have been no well-designed randomised control trials (RCT) on treatment by coil embolization which is now a popular form of treatment in the private sector.

Our study shows that women with PVI have a distinctive symptom profile with the most notable features being the presence of dull pelvic pain that radiates to the
upper thighs and aggravated by prolonged standing and walking. Surprisingly, this pain was present throughout the month, and related to menstruation and sexual intercourse. These symptoms are most typical of those we would expect from engorged veins and are similar to the leg symptoms experienced by patients with severe VV's.

How PVI impacts HR-QoL has never been reported previously. We found women with PVI to report a lower HR-QoL than healthy controls due to pelvic and thigh pain. That PVI subjects did not visit their GP more frequently may be explained by studies reporting that more than a quarter of women with CPP in the community do not seek medical attention. Women with CPP either view this discomfort as ‘normal’ or withdraw from seeking help despite continued symptoms.

An adequately powered epidemiological study to compare the frequency of PVI in women with and without CPP is now needed. If PVI is more prevalent in women with CPP then an RCT to explore whether popular treatments such as trans-venous occlusion for PVI reduces symptoms of pelvic pain and improves quality of life in women with PVI and CPP would be justified.

**Chapter summary**

Women with PVI reported more pelvic pain and were greater users of NHS resources than both matched VV and healthy controls. Quality of life was lower in women with PVI compared with healthy controls. Patients describe a distinctive pelvic and thigh pain which should aid diagnosis in the future. Research into the prevalence of PVI in women with CPP and an RCT evaluating trans-venous occlusion in the treatment of women with PVI and CPP are needed.
CHAPTER 5: DIAGNOSIS OF PELVIC VEIN INCOMPETENCE USING MINIMALLY-INVASIVE ULTRASOUND TECHNIQUES

This chapter is published in Vascular 2016; Online Print DOI: 10.1177/1708538116670499

Abstract

**Background:** Pelvic vein incompetence (PVI) is a cause for pelvic pain and recurrent varicose veins in women. The reference standard diagnostic method is reflux venography involving radiation, nephrotoxic contrast and jugular puncture. Trans-vaginal ultrasound (TVU) is increasingly being used as a diagnostic tool for PVI.

**Methods:** 50 women with clinical suspicion of PVI and aged between 18-55 years were recruited over two years at a large UK University Teaching Hospital. TVU was performed using a standardised protocol which included assessment of the ovarian and internal iliac veins bilaterally in the supine and semi-standing position with provocative manoeuvres. Diagnostic readability and inter-observer variability was determined.

**Results:** Mean (range) age of 43 (23-51). Visibility of all four pelvic veins was better in the supine position compared with semi-standing (76% vs. 64%). PVI was identified in 34 of 50 (68%) women in the supine position compared with 38 of 50 (76%) women in the semi-standing position. PVI was demonstrated in 35 of 50 (70%) women with Valsalva manoeuvre. Inter-observer variability was 0.84 (kappa, very good agreement, p=0.001).

**Conclusion:** TVU is effective at demonstrating PVI. All TVU protocols should include assessment of pelvic veins in the supine and semi-standing position with Valsalva manoeuvre.
Introduction

First identified in 1949 PVI is becoming increasingly recognised as a cause for both chronic pelvic pain in women and recurrent varicose veins of the leg. Despite being thought to affect between 15-20% of women, PVI is still rarely diagnosed in the United Kingdom and is often missed on diagnostic laparoscopy as patients are tilted head-down, leading to the pelvic veins to empty and is not routinely looked for in most venous units investigating causes for recurrent varicose veins of the leg. Studies have shown one in five women presenting with varicose veins to have reflux of non-saphenous origin.\(^74\) \(^83\)

Pelvic vein embolization is a popular form of treatment for PVI.\(^{119}\)\(^{120}\) Immediately prior to pelvic vein embolization women undergo reflux venography in which pelvic veins are cannulated using a metallic guide wire via jugular puncture and contrast injected under X-ray guidance to determine the size of the vein and direction of flow.\(^{56}\)\(^{102}\)\(^{121}\) It is an invasive diagnostic procedure involving a jugular puncture, radiation and nephrotoxic contrast performed in young premenopausal women. The amount of radiation women are exposed to during the procedure is equivalent to 1-3 years of exposure to background radiation in the UK and is estimated to cost approximately £413.31 per episode to the NHS.

TVU is growing in popularity as a non-invasive, safe alternative to reflux venography.\(^{122}\)\(^{124}\) It has been shown to be an excellent imaging modality in identifying distal ovarian and iliac veins, uterine venous plexuses, haemorrhoids and vulval varicose veins.\(^{122}\)\(^{125}\) Despite this, a standardised protocol has never been developed and several centres practice their own protocol, leading to poor reproducibility and comparison.\(^74\) \(^93\)

The aim of this study was to establish the best method of reproducing PVI using TVU and to formulate a standardised protocol that can be universally used and compared with the current reference standard. We also assess the level of diagnostic readability and inter-observer reproducibility of TVU for PVI detection.
Methods

Participants and setting

Women seen in the varicose vein clinic between September 2013 to September 2015 with a leg vein pattern which suggests communication to the pelvic veins were invited to undergo a trans-vaginal ultrasound to determine the presence of PVI. Indications for TVU included: vulval varices, posterior thigh or buttock varices and recurrent varicose veins of the leg.

Inclusion criteria included being female aged between 18-55 and pre-menopausal. Exclusion criteria were i) post-menopausal, ii) pregnant or within 12 months of pregnancy iii) history of venous thromboembolism, ischaemic heart disease or stroke iv) hysterectomy v) BMI >40 vi) unable to give informed consent.

All participants were recruited from a large University Teaching Hospital in the UK and all the TVU scans was performed by one of two accredited vascular technologists. The vascular technologist was blinded to the participant’s clinical history.

TVU Protocol

We developed a standardised protocol for the detection of PVI using TVU. The trans-vaginal duplex probe (Phillips iU22 scanner with C10-3v purewave transducer) was introduced into the vagina with the patient in a supine position. The patient is asked to empty their bladder prior to the study. Flow optimisation to image low flow is adjusted manually as required. The Doppler sample volume is adjusted manually when measuring vein volume. The presence of reflux in the ovarian, internal iliac and para-uterine veins on both sides was assessed in the following positions as shown in figure 16:

1) supine position with quiet respirations
2) supine position with Valsalva manoeuvre
3) semi-erect position (patient sat on the edge of the examination couch with their legs dependent and feet on the floor) with quiet respirations
4) semi-erect position with Valsalva manoeuvre
5) semi-erect position with two-handed thigh compression and release

Sustained reverse flow of >0.5 seconds is reported as venous incompetence (or reflux) in varicose veins of the leg; therefore we have adopted the same diagnostic cut-off for PVI. Reflux in one or more veins will be classed as PVI. Vein diameter was also recorded although no figure was used as a cut-off for the diagnosis of PVI. Each vein was assessed until the sonographer was satisfied. Valsalva manoeuvre was standardised as forceful attempt at exhalation against a closed glottis. Participants were asked to blow into a 20ml syringe for 3-5 seconds. Thigh compression and released was performed by an assistant using a firm two-handed squeeze around the upper thigh which was quickly released.

Figure 16 Illustration of the supine and semi-erect positions used for Doppler TVU
**Diagnostic Readability**

Static images recorded during the TVU for all the women who underwent a scan for the detection of PVI during the study period were identified on an electronic medical images archive system (Synedra View Personal 3 version 3.4.0.2). Images of individual veins with and without PVI were anonymised and collated. Two blinded vascular technologists were then asked to review the images and record them as ‘PVI’ ‘No PVI’ or ‘equivocal’.

**Inter-observer variability**

All women consenting to take part in this study were invited to undergo a repeat TVU by a second independent vascular technologist in the same sitting. Both vascular technologists were blinded to the results of their colleagues scan and to the patient’s clinical history. The vascular technologists each performed the same TVU protocol and documented on the presence of pelvic vein reflux.
Acceptability

Participants were asked to complete a seven-point questionnaire on the acceptability of the ultrasound scan. Designed by the research team, participants were asked whether they found the scan and the changing positions comfortable, uncomfortable or embarrassing. Participants were also asked how the scan had compared with previous internal examinations they may have had in the past, and whether they would have it again in the future if required.

Data Analysis

Statistical analysis was performed using SPSS versions 20 (SPSS, Chicago, Illinois, USA). Frequency of reflux was compared using simple descriptive statistics. Patient position and detection of reflux were ranked and compared between the groups using chi-square linear trend test. Spearman's correlation coefficient was used to measure the strength and direction of association between reflux time and vein diameter. Data was recorded and analysed using SPSS (IBM SPSS Statistics Version 22).

Contingency tables (crosstabs) and percentage total agreement and Cohen's kappa coefficient was used to determine the readability and inter-observer reproducibility. The kappa coefficient was interpreted to identify the strength of agreement along. P value <0.05 was deemed statistical significance.

Local ethics committee approval was obtained (reference 12/NW/0761). All potential participants were provided with study information leaflets and written consent was obtained.

No formal sample size calculation was performed as this is an exploratory study and the number of participants attending for assessment of PVI was infrequent and thought to be small; therefore consecutive participants were recruited on attending clinic over the study timeframe.
Results

In total, 59 women were referred for trans-vaginal ultrasound over the 24-month period. All patients were referred to the study from the vascular or varicose vein clinic. In total 50 of 59 (84%) met eligibility criteria and underwent a TVU using the described protocol. A total of 45 of 50 (90%) women consented to having images saved to be anonymised and reviewed as part of this study. A further 14 of 50 (28%) agreed to undergo two TVU scans by two independent and blinded Vascular Technologists (Figure 17). Mean (range) age for this group was 43 (23-51). Mean (SD) body mass index (BMI) was 23 (7). A total of ten women from this cohort were shown to have PVI and underwent treatment by trans-venous occlusion. This is discussed in more detail in Chapter 6.

Figure 17 Flow diagram of study participants

- 59 women referred to study
- 9 women excluded: 3 post menopausal, 3 post hysterectomy, 2 post-partum, 1 refused to undergo TVU
- 50 women meet eligibility criteria and undergo TVU
- 14 underwent two independent scans
- 45 had images saved and reviewed
- 10 women were referred for reflux venography (Chapter 6)
Visibility

In each scan four veins were isolated in the two positions; the left ovarian vein (LOV), right ovarian vein (ROV), left internal iliac vein (LIIV) and the right internal iliac vein (RIIV). In the supine position, 38 of 50 (76%) women had all four veins identified, compared with 32 of 50 (64%) women in the semi-standing position (table 6). The most common reason for veins to be unidentifiable was excessive bowel gas, or difficulty manoeuvring the ultrasound probe into the lateral fornixes which was more common during the semi-standing position.

Table 6 Frequency that each vein was visible in the two positions

<table>
<thead>
<tr>
<th></th>
<th>Supine (n,% )</th>
<th>Semi-standing (n,% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ovarian vein</td>
<td>43/50 (86%)</td>
<td>36/50 (72%)</td>
</tr>
<tr>
<td>Right ovarian vein</td>
<td>44/50 (88%)</td>
<td>29/50 (58%)</td>
</tr>
<tr>
<td>Left internal iliac vein</td>
<td>49/50 (98%)</td>
<td>44/50 (88%)</td>
</tr>
<tr>
<td>Right internal iliac vein</td>
<td>45/50 (90%)</td>
<td>43/50 (86%)</td>
</tr>
</tbody>
</table>

Diameter

Mean (sd) diameter of each vein in the supine and semi-standing position is shown in table 7. In all four veins assessed the vein diameter increased on semi-standing. Correlation between diameter and reflux time was examined. LOV and ROV diameter in the supine position was well correlated with reflux time (Spearman’s coefficient=0.451, p<0.001 and Spearman’s coefficient=0.609, p<0.001 respectively), whereas LIIV and RIIV diameters did not correlate with reflux time.
Table 7 Median (range) vein diameter in the supine and semi-standing positions

<table>
<thead>
<tr>
<th></th>
<th>LOV</th>
<th>ROV</th>
<th>LIIV</th>
<th>RIIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>5(2-11)mm</td>
<td>5(3-14)mm</td>
<td>8(3-17)mm</td>
<td>7(3-14)mm</td>
</tr>
<tr>
<td>diameter in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>supine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>6(4-13)mm</td>
<td>6(3-8)mm</td>
<td>10(4-16)mm</td>
<td>9(4-14)mm</td>
</tr>
<tr>
<td>diameter in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-standing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Identifying PVI

PVI was identified in 34 of 50 (68%) women in the supine position, and in 38 of 50 (76%) women in the semi-standing position. In 11 of the 50 (22%) women PVI was seen in the supine position initially, but when changed to the semi-standing position no PVI was demonstrated. In reverse, 14 of 50 (28%) women had no PVI in the supine position but demonstrated PVI when examined in the semi-standing position. Table 8 below illustrates how the changing position impacts the frequency of reflux detected. Taking into consideration the LOV, reflux was demonstrated in both the supine and semi-standing position in 11 of 50. In 10 of the 50 women, reflux was seen in the supine position only, and in another five women it was seen on semi-standing only.
Table 8 The frequency of reflux in the two positions

<table>
<thead>
<tr>
<th></th>
<th>LOV (n=50)</th>
<th>ROV (n=50)</th>
<th>LIIV (n=50)</th>
<th>RIIV (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PVI detected</td>
<td>19 (38%)</td>
<td>24 (48%)</td>
<td>24 (48%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>PVI seen in the</td>
<td>10 (20%)</td>
<td>10 (20%)</td>
<td>5 (10%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>supine position only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVI seen in the</td>
<td>5 (10%)</td>
<td>9 (18%)</td>
<td>4 (8%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>semi-standing position only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstrated in both</td>
<td>11 (22%)</td>
<td>3 (6%)</td>
<td>16 (32%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Vein not visible</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Effects of Valsalva manoeuvre

When assessing individual veins seen (and not participants) Valsalva was used in both the supine and semi-standing positions (table 9). When compared with quiet respirations which demonstrated PVI in only 10 of 200 (5%) individual veins assessed, Valsalva demonstrated PVI in 141 of 200 (71%) veins.

Table 9 Frequency of PVI using provocative manoeuvres compared with quiet breathing

<table>
<thead>
<tr>
<th></th>
<th>LOV Supine</th>
<th>LOV Semi-standing</th>
<th>ROV Supine</th>
<th>ROV Semi-standing</th>
<th>LIIV Supine</th>
<th>LIIV Semi-standing</th>
<th>RIIV Supine</th>
<th>RIIV Semi-standing</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reflux seen</td>
<td>20 (40%)</td>
<td>19 (38%)</td>
<td>25 (50%)</td>
<td>20 (40%)</td>
<td>27 (54%)</td>
<td>22 (44%)</td>
<td>28 (56%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Reflux at rest</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Reflux during</td>
<td>18 (36%)</td>
<td>14 (28%)</td>
<td>17 (34%)</td>
<td>14 (28%)</td>
<td>22 (44%)</td>
<td>21 (42%)</td>
<td>13 (26%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Valsalva</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not visible</td>
<td>7 (14%)</td>
<td>14 (28%)</td>
<td>6 (12%)</td>
<td>14 (28%)</td>
<td>1 (2%)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
<td>9 (18%)</td>
</tr>
</tbody>
</table>
Effect of thigh-compression and release

Two-handed thigh compression and release was performed in all 50 women during the semi-standing position. Reflux of the LIIV was demonstrated by thigh compression and release in one participant in the semi-standing position. This reflux had already been demonstrated by Valsalva manoeuvre in both the supine and semi-standing.

Observer readability

45 of 50 (90%) women consented to have images at the time of scanning recorded to view at a later date on the electronic database system. Total agreement amongst the two-blinded vascular technologists in diagnosing PVI was seen in 32 cases (71%) with disagreement seen on 13 cases (29%). Of these 13 cases in which there was disagreement, 8 were diagnosed as PVI by observer one. The remaining 5 of 13 were graded as equivocal. A Cohen’s kappa coefficient of 0.48 showed moderate agreement but a p-value of <0.001 proved the coefficient to be statistically significant (table 10).

<table>
<thead>
<tr>
<th>Observer 2</th>
<th>PVI (n, %)</th>
<th>No PVI (n, %)</th>
<th>Equivocal (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVI (n, %)</td>
<td>18 (40%)</td>
<td>4 (9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>No PVI (n, %)</td>
<td>3 (7%)</td>
<td>14 (31%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Equivocal (n, %)</td>
<td>2 (4%)</td>
<td>3 (7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>n</th>
<th>% total agreement</th>
<th>Kappa coefficient</th>
<th>P value</th>
<th>Strength of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>71.1%</td>
<td>0.48</td>
<td>P&lt;0.001</td>
<td>Moderate agreement</td>
</tr>
</tbody>
</table>
Inter-observer variability

14 of the 50 (28%) women consented to have two trans-vaginal ultrasound scans by two independent and blinded sonographers. Total agreement of PVI diagnosis was seen in 13 of 14 women (93%). One case was identified to have PVI by observer 1 which was disputed by observer 2 (table 11). A kappa coefficient of 0.84 demonstrated very good agreement with a P value of 0.001. Individual agreement between the veins identified as refluxing occurred in 7 of the 14 patients (50%).

Table 11 Inter-observer variability of PVI diagnosis amongst two blinded vascular technologists

<table>
<thead>
<tr>
<th>Observer 1</th>
<th>Observer 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PVI (n, %)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>No PVI (n %)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>PVI (n, %)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>No PVI (n %)</td>
<td>4 (29%)</td>
</tr>
</tbody>
</table>

Acceptability

All 50 women found being examined in the supine position comfortable, compared with 41 of 50 (82%) women finding the semi-standing position comfortable. Discomfort was often reported during the transition from supine to a semi-standing position.

In total, 45 of 50 (90%) had undergone a trans-vaginal ultrasound in the past. Of these subjects, 39 of 45 (87%) reported it to be better than their previous experience, and 6 of 45 (13%) women reported it was the same as previous experiences. None of the women commented that the trans-vaginal ultrasound was worse than previous experiences. All 50 women reported that they would have the examination again in the future if it was required.
Discussion

This study has demonstrated that PVI can be successfully identified using ultrasound. The scanning protocol used in future studies should incorporate assessment of the pelvic veins in the supine and semi-standing position with Valsalva manoeuvre. Thigh compression and release does not improve the rate of reflux demonstrated. Women find the protocol acceptable and it compared favourably to previous TVU scans performed for pelvic pain. We suggest that this protocol is followed in all centres investigating for PVI, allowing for future comparison and reproducibility.
Ultrasound is frequently used for the investigation of venous and arterial disease. Very good agreement was seen in inter-observer variability between two blinded vascular technologists. This is similar to the agreement observed for the diagnosis of varicose veins (kappa of 0.77) or deep vein thrombosis (kappa of 0.92). Although the agreement was very good in the overall diagnosis of PVI versus no PVI, when examining the individual results of the scans, only 7 of the 14 (50%) women had identical scan results, of which four were ‘No PVI’. This suggests TVU may be more appropriate as a screening tool to be used before reflux venography rather than a diagnostic tool to direct treatment. However until we have information on the sensitivity and specificity of TVU in diagnosis PVI, it cannot be used in a clinical context.

Our results correlate with existing research in demonstrating that incompetent veins have a larger diameter than competent veins. However no strong correlation was seen between diameter and the presence of reflux. This is consistent with previous studies which have demonstrated that the size of the ovarian or saphenous vein cannot be used an indicator of venous reflux. However many clinicians still use vein size to plan invasive treatment of PVI despite this evidence.

Reflux was frequently seen in the supine position which then disappeared on semi-standing. This does suggest that competent veins may demonstrate reflux in the supine position as there is no strong gravitational force to maintain valve closure. In the semi-standing position competent valves will counter the effects of gravity and incompetent valves put under pressure by gravity or Valsalva will demonstrate reflux. Ultrasounds who demonstrate reflux in supine which is not visible on semi-standing are deemed equivocal and may warrant either repeat ultrasound or assessment by venography (retrograde or MR) to clarify the findings. The diagnostic flow chart is shown in Figure 18.

The strength of this study was the robust TVU protocol used, which allowed for direct comparison between positions and provocative manoeuvres. A limitation of this study is the diagnostic readability was determined using still images that did not allow for measurement of the reflux waveform which would have provided a more accurate assessment. TVU will need to be directly compared against reflux venography in women who have had both investigations to determine its accuracy.
Despite the advantages of ultrasound, TVU requires a degree of experience on the part of the sonographer and so the outcome of the investigation may differ depending on the operator's skill. The 0.5-second reflux time cut-off for the diagnosis of PVI is based on clinical experience, expert opinion and is the standardised cut-off in assessment of superficial vein reflux of the leg. However in the assessment of deep vein reflux of the leg the standard cut-off used is one second; this may more appropriate in the diagnosis of PVI as it would reduce the chances of the artefact being interpreted as reflux and therefore reduce the risk of over-diagnosing PVI. A limitation of this study was not recording reproducibility of vein diameters as well as the presence of reflux. However diameters can vary depending on where on the vessel isonation occurs and on probe position where as reflux is often seen constantly down the entire vein.

TVU is relatively inexpensive to perform and safe, avoiding exposure to radiation or contrast to radiosensitive ovaries. It allows for assessment of pelvic vein diameter and direction of flow as an accurate screening tool. Further research is needed to evaluate the intra-observer variability and reproducibility. Further studies are also needed to compare TVU with the reference standard tests such as reflux venography or the less invasive and safer MR venography.

**Chapter summary**

TVU is an effective screening tool at demonstrating PVI in women. It is relatively cheap, safe and quick to perform. Patients also find it comfortable and acceptable. All TVU protocols are recommended to include assessment of pelvic veins in the supine and semi-standing position with Valsalva manoeuvre. The accuracy of TVU needs to be confirmed by direct comparison with reflux venography.
CHAPTER 6: DETECTING PELVIC VEIN INCOMPETENCE IN WOMEN-ACCURACY OF TRANS-VAGINAL DUPLEX ULTRASOUND COMPARED TO REFLUX VENOGRAPHY

This manuscript has been prepared for submission to a peer-reviewed journal

Abstract

Background: Pelvic vein incompetence (PVI) is usually diagnosed by reflux venography. This is invasive, involves nephrotoxic contrast and ionizing radiation in young women of childbearing age. Trans-vaginal duplex ultrasound (TVU) is a safe alternative however it has not been compared against the reference standard. We compare the accuracy of TVU with reflux venography for the detection of PVI.

Methods: Twenty-two women with clinical suspicion of PVI who underwent TVU and reflux venography were included in this study. Sensitivity, specificity, positive and negative predictive value were calculated for TVU using reflux venography as the reference standard.

Results: Paired TVU and reflux venography images were analysed from 22 women with a mean (range) age of 45 (25-55). PVI was detected in all 22 images with TVU and 21 of 22 (95%) images with reflux venography. TVU identified left ovarian vein incompetence in 15 vs 16 by reflux venography, right ovarian incompetence 6 vs 9, left internal iliac vein 12 vs 12 and right internal iliac vein 9 vs 10.

Conclusion: TVU is possibly an appropriate alternative to reflux venography in the detection of PVI however accuracy could not be determined through this study design. Women with negative TVU must be evaluated using reflux or MR-venography to determine sensitivity and specificity before it can be considered as a screening or diagnostic tool.
Introduction

Chronic pelvic pain (CPP) is a major health problem accounting for over 20% of all gynaecology outpatient appointments in the United Kingdom and affecting approximately 24% of women of childbearing age.64 CPP reduces health-related quality of life and is a leading cause of physical, psychological and emotional distress.10 Over 50% of women with CPP undergo invasive investigations and procedures and never obtain a cause for their symptoms. Pelvic vein incompetence is becoming increasingly recognised as a cause for CPP and innovative methods of its diagnosis and treatment are being evaluated. Women with symptoms of pelvic pain and PVI found on imaging are often referred as having ‘pelvic congestion syndrome’.

Several methods of diagnosing PVI have been evaluated. This includes trans-abdominal and trans-vaginal ultrasound, CT, MRI and reflux venography which is often referred as the reference standard.60 The commonly used diagnostic laparoscopy for CPP is often not helpful as patients are tilted head-down leading the pelvic veins to empty.46

TVU allows better visualisation of the pelvic organs and vessels providing a better assessment of pelvic vein diameter and flow direction. It can also be performed in the supine and semi-standing position with additional provocative manoeuvres to exaggerate reflux.74 CT and MRI are both non-invasive imaging techniques that allow complete examination of the pelvic anatomy with multi-planar imaging. Both modalities can identify enlarged pelvic veins and provide information regarding existing pathology. CT however does involve radiation and MRI cannot be used to follow up patients after coil occlusion due to metallic artefact. Both CT and MRI are conventionally performed in the supine position, which can lead to under-filling of the pelvic veins.59

Reflux venography is an invasive procedure performed immediately before embolization. Pelvic veins are cannulated using a metallic guide wire via a jugular vein puncture under fluoroscopic guidance and contrast injected to determine the
size of the vein and flow direction. It can be performed in both the supine and semi-upright position with Valsalva manoeuvre.

The aim of this prospective study was to assess the clinical utility and accuracy of trans-vaginal Doppler ultrasound (TVU) compared with reflux venography in the detection of PVI in patients undergoing coil embolisation.
Methods

Participants and Setting

This prospective observational study was conducted at a single tertiary referral vascular centre in the United Kingdom. Women aged between 18-55 with clinical suspicion of PVI or pelvic congestion syndrome were referred to this vascular centre from gynaecologists and vascular surgeons from within the region. Indications for referral included recurrent varicose veins of the leg with incompetence suggested to be of pelvic origin, vulval varices, posterior thigh or buttock varices, a history of pelvic pain and patients who have been shown to have PVI on alternative imaging such as CT, MRI or diagnostic laparoscopy.

Inclusion criteria included being female aged between 18-55 and pre-menopausal. Exclusion criteria were i) post-menopausal, ii) pregnant or within 12 months of pregnancy iii) history of venous thromboembolism, ischaemic heart disease or stroke iv) hysterectomy v) BMI >40 vi) unable to give informed consent.

Over a 24-month period, 56 consecutive women were referred for the investigation and potential treatment of PVI. A total of 42 of 56 (75%) women met the eligibility criteria and 35 women underwent a TVU scan. Three women (9%) did not attend their appointment, and a further four women (11%) did not have PVI identified on TVU. A total of 22 of 56 (39%) women underwent a TVU which demonstrated PVI and were then referred for reflux venography and coil occlusion.

Ten of the 22 women had been recruited to a previous study described in Chapter 5 before being referred to under reflux venography as part of their clinical care and were followed up as part of this study. Only women with PVI detected on TVU were referred for reflux venography and coil occlusion. Local ethics committee approval was obtained (reference 15.NW.0360).
Trans-vaginal duplex ultrasound (TVU)

All TVU investigations were performed in both supine and semi-standing positions by the same experienced vascular scientist. A trans-vaginal duplex probe (Phillips iU22 scanner with C10-3v purewave transducer) was introduced into the vagina and the internal iliac and ovarian veins on each side were isonated, the diameter measured (mm) and the presence of dilation or tortuous veins around the ovaries and uterus recorded. PVI was defined as sustained reflux >0.5 seconds generated by Valsalva. The TVU was not performed to determine any additional intra-abdominal or pelvic pathology.

Reflux venography

A 6-French sheath was placed in the right internal jugular vein under local anaesthetic and ultrasound guidance. Internal jugular vein access was preferred by the clinicians at this centre over femoral vein access because it provided easier access to the right ovarian vein and allowed for quicker mobilisation and discharge compared with femoral vein puncture which would require patients to stay supine for up to four hours.

Both the left and right ovarian veins and bilateral internal iliac veins were selectively catheterized with a 5.2 French catheter. All venogram images were acquired with the patient supine and semi-erect by tilting the table head up. Retrograde flow for more than 0.5 seconds was reported as venous incompetence. All reflux venography assessments were performed by one of three Consultant Vascular Interventional Radiologists.

Statistical Analysis

Demographic data was collected and all images were reported by either an accredited vascular laboratory technologist or a Consultant Vascular Interventional Radiologist. The detection of PVI by TVU and reflux venography
were compared with reflux venography being considered the reference standard. Adverse events and complications were also recorded. Comparison of frequencies was performed and measures of accuracy relating to incompetence detection (categorical variable) including sensitivity, specificity, positive and negative predictive values were calculated using contingency tables and SPSS versions 20 (SPSS, Chicago, Illinois, USA).
Results

Forty-four paired TVU and reflux venography images were analysed from 22 women who underwent both TVU and reflux venography. Mean (range) age of subjects was 45 (25-55). The interval between paired images was 6.6 ± 5.7 (mean ± SD) months. PVI was detected in all 22 (100%) TVU scans as this was a prerequisite prior to undergoing reflux venography. PVI was detected in 21 of the 22 (95%) on reflux venography.

TVU identified 15 of 22 (68%) women to have left ovarian vein (LOV) incompetence compared with 16 of 22 (73%) identified by reflux venography (table 12). Right ovarian vein (ROV) incompetence was seen in 6 of 22 (27%) women by TVU compared with 9 of 22 (41%) women by reflux venography. Left internal iliac vein (LIIV) incompetence was seen in 12 of 22 (55%) women by TVU compared with 12 of 22 (55%) women by reflux venography. Right internal iliac vein (RIIV) incompetence was seen in 9 of 22 (41%) women by TVU, compared with 10 of 22 (45%) women by reflux venography. Although the overall sensitivity and specificity could not be determined, individual vessel identification and diagnosis was compared (table 12).

No complications or adverse events were recorded after TVU or reflux venography. Eight of the 22 (36%) women undergoing reflux venography could not have all four veins catheterized due to tortuosity or significant vasospasm.
Table 12 Frequency of PVI detected with accuracy

<table>
<thead>
<tr>
<th></th>
<th>TVU (n=22)</th>
<th>Reflux venography (n=22)</th>
<th>Sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOV</td>
<td>15</td>
<td>16</td>
<td>Sensitivity 81.25% (95% CI 54.45 to 96.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity 66.7% (95% CI 22.7 to 94.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV 84.7% (95% CI 54.5 to 98.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV 57.1% (95% CI 18.4 to 90.1)</td>
</tr>
<tr>
<td>ROV</td>
<td>6</td>
<td>9</td>
<td>Sensitivity 66.7% (95% CI 29.9 to 92.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity 100% (95% CI 75.3 to 100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV 100% (95% CI 54.1 to 100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV 81.3% (95% CI 54.4 to 96)</td>
</tr>
<tr>
<td>LIIV</td>
<td>12</td>
<td>12</td>
<td>Sensitivity 91.7% (95% CI 61.5 to 98.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity 90% (95% CI 55.5 to 99.8)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PPV 91.7% (95% CI 61.5 to 99.8)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NPV 90% (95% CI 55.5 to 99.8)</td>
</tr>
<tr>
<td>RIIV</td>
<td>9</td>
<td>10</td>
<td>Sensitivity 70% (95% CI 34.8 to 93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity 83% (95% CI 55.5 to 98.3)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PPV 77.8% (95% CI 47.4 to 97.9)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NPV 75% (95% CI 42.4 to 94.2)</td>
</tr>
</tbody>
</table>
Discussion

This study reports on whether reflux venography agrees with the diagnosis of PVI on TVU. Fair individual agreement was seen which may support the potential future use of TVU as a diagnostic or screening tool for women with CPP. When comparing the individual veins assessed by either modality, both reported similar frequencies and sensitivities ranged from 70-92% and specificity from 66-100%.

A thorough scope of the literature highlighted only a handful of small studies assessing ultrasound in the diagnosis of PVI. A study by Beard et al found pelvic ultrasound to diagnose PVI with a sensitivity of 94% when compared with trans-uterine venography in 41 women but with poor individual agreement. Barros et al demonstrated a sensitivity of 96% and specificity of 100% of pelvic Doppler ultrasound and phlebography in 54 women.

Study strength includes the direct comparison between both imaging modalities in women with clinical suspicion of PVI with a short time interval between both imaging assessments. All subjects were attendees to a tertiary vascular referral centre and TVU was performed by one accredited vascular technologist.

A significant limitation of this study was the fact only women with TVU positive for PVI were referred for assessment by reflux venography. This evidently means the study is at significant risk of partial-verification bias and both sensitivity and specificity of TVU could not be calculated. In order to reduce this risk of partial-verification bias, future studies could either subject women with normal TVU results to reflux venography, or compare TVU with a non-invasive alternative such as MR venography to determine data on specificity and sensitivity. Subjecting women with normal TVU to reflux venography may be deemed unethical as it does involve risks of obtaining central venous access and high-dose radiating. A further limitation was the small sample size. This is primarily due to the small number of patients who received approval for treatment of PVI by the NHS Commissioning body as PVI treatment is currently not widely available on the NHS.

Although TVU is unable to determine abdominal pathology as effectively as trans-abdominal ultrasound or CT/MRI, often patients with CPP undergo extensive
invasive and non-invasive diagnostic procedures such as laparoscopy and pelvic ultrasound which will reliably identify abdominal pathology if present. Compression of the left renal vein (referred to as Nutcracker Syndrome) is rare and not routinely screened for. TVU can also be performed with the patient in the semi-standing position which allows for a good comparison with reflux venography performed in the semi-erect position.

The diagnosis of PVI on reflux venography requires standardisation. A wide range of techniques exist for performing the procedure and the diagnosis criteria is often based on experience or anecdotal evidence rather than robust clinical evidence. A recent national survey amongst clinicians treating women with PVI identified discordance in opinions in how it should be diagnosed and when reflux venography should be performed. The method of occlusion and technique used was also shown to be based on experience. On entering discussions regarding reflux venography reporting and the criteria used for its diagnosis with several regional Vascular Interventional Radiologists, it became apparent that there is no agreed diagnostic criteria or technical protocol. A Delphi study has been initiated by the research group to provide expert consensus on this.

Reflux venography is often performed immediately before treatment by coil occlusion. Therefore it is important to ensure 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.
**Chapter summary**

TVU may represent an appropriate and safe alternative to reflux venography in the diagnosis of PVI but this study failed to evaluate its accuracy at diagnosing PVI. Since all the participants in this study had positive TVU scans, it was exposed to significant partial-verification bias preventing any formal conclusion about its use as a screening or diagnostic tool. TVU will need to be compared with non-invasive imaging such as MR venography in order to determine its diagnostic accuracy without bias. It is inexpensive and quicker to perform than reflux venography which although widely used, is still an un-standardised test no robust technical protocol or diagnostic criteria.
CHAPTER 7: IS THERE A RELATIONSHIP BETWEEN PELVIC VEIN INCOMPETENCE AND CHRONIC PELVIC PAIN? A CASE CONTROL STUDY

This manuscript has been prepared for submission to a peer-reviewed journal

Abstract

Background: CPP is a major health problem affecting millions of women worldwide and over 40% of women fail to achieve a diagnosis despite repeated hospital admissions and invasive tests. PVI is suggested to be a cause for CPP but existing literature has shown it to be present in both women with and without pain. The aim of this study is to determine whether there is an association between PVI and CPP in women.

Methods: A case-control study was performed across three UK teaching hospitals over a two-year period. Cases were premenopausal women diagnosed with CPP and were reported to have a normal diagnostic laparoscopy. Controls were premenopausal women with no medical history or diagnosis of chronic pelvic pain were matched for age and parity within two years to each case. These control women were recruited over the same two-year period using snowball sampling and local advertisement.

Results: 35 cases-controls pairs (70 women in total) were matched for age and parity. Mean age (range) was 34.5 (22-47) for the CPP cases compared with 34.5 (19-52) for the healthy controls. Women with CPP had a PVI prevalence of 46% compared with 20% in healthy controls, p=0.02. When comparing health status and pain symptoms, no significant difference could be determined between women with CPP and PVI compared with women with CPP alone.

Conclusion: PVI is strongly associated with women with CPP. Although association does not imply causation, further research into PVI as a cause of pelvic pain is warranted.
Introduction

Defined as continuous or intermittent lower abdominal or pelvic pain of at least six months duration (not occurring exclusively with menstruation, intercourse and pregnancy), CPP is widely accepted to be a major health problem. It primarily affects younger women, causing disruption to their daily lives, social isolation, relationship difficulties and loss of work-related productivity.\(^1\)

Annual treatment costs in the UK were estimated to be £182 million/year in 1992 with little recent data.\(^2\) This is likely to be substantially higher now, with the US costs of managing CPP estimated at well over $100 billion/year. Approximately 38 per 1000 women attend primary care with CPP each year, a rate comparable with migraine, asthma and back pain.\(^{132}\) They are usually referred to a gynaecologist (accounting for 20% of referrals) and undergo repeated hospital admissions with invasive investigations such as diagnostic laparoscopy or even hysterectomy.

PVI has been suggested as a cause for CPP in women and many pursue investigation and treatment of PVI at great personal cost without strong evidence demonstrating an association or causal relationship between PVI and CPP. It is important and timely that the relationship between PVI and CPP is explored in a robust case-control study. If a significant association between PVI and CPP is found, it will enable clinicians to focus their investigations, reducing the need for expensive and often invasive procedures. Demonstrating no association between PVI and CPP would reduce the need for women to seek investigations and treatments for PVI. The results of this study will have immediate applicability to guide decision-making, and the investigation and treatment of women with debilitating pelvic symptoms.

The aim of this case-control study is to determine the prevalence of PVI detected by trans-vaginal ultrasound in women with and without chronic pelvic pain.
Methods

Participants and settings

Premenopausal women aged between 18-49 years diagnosed with CPP and reported to have a normal laparoscopy result were recruited prospectively over a two-year period from the gynaecology clinics at two UK hospitals (University Hospital of South Manchester and Central Manchester Foundation Trust). A further cohort of premenopausal women aged between 18-49 years with no medical history or diagnosis of CPP were matched for age and parity within two years to each case. These control women were recruited over the same two-year period using snowball sampling (asking existing study subjects to recruit future subjects from among their acquaintances) and recruitment by local advertisement.

Exclusion criteria was i) post-menopausal ii) pregnant or within 12 months of pregnancy iii) history of venous thromboembolism, ischaemic heart disease or stroke iv) history of heart, renal or liver failure v) any diagnosis or treatment for malignancy within 12 months vi) hysterectomy vii) body mass index (BMI) >40 or viii) unable to give informed consent.

Local ethics committee approval was obtained (reference 13/NW/0227). All potential participants were provided with study information leaflets and written consent was obtained.

Trans-vaginal ultrasound

All TVU investigations were performed in both supine and semi-standing positions by the same experienced vascular scientist. A trans-vaginal duplex probe (Phillips iU22 scanner with C10-3v purewave transducer) was introduced into the vagina and the internal iliac and ovarian veins on each side were isonated, the diameter measured (mm) and the presence of dilation or tortuous veins around the ovaries and uterus recorded. The TVU was not performed to determine any additional intra-abdominal or pelvic pathology.
PVI was defined and diagnosed when sustained reflux >0.5 seconds generated by Valsalva was identified.

**Symptoms and quality of life score**

All subjects were asked to complete a structured questionnaire on symptoms, health related quality of life and use of healthcare resources.

Despite a diligent search, we failed to identify a single existing questionnaire or disease specific outcome measure which adequately captured issues relevant to both PVI and CPP. Under the guidance of our PPI group, a health questionnaire was designed by extracting validated questions from several well-known outcome measures. Although not validated, this customised health questionnaire served to collect information regarding pain symptoms and their broader impact on subjects. Questions used in the customised health questionnaire were selected from the following validated scores: i) International Pelvic Pain Society assessment form,\textsuperscript{28} ii) the Endometriosis Health Profile (EHP-30),\textsuperscript{109} iii) the British Society of Gynaecological Endoscopy (BSGE) pelvic pain questionnaire,\textsuperscript{110} iv) the heavy menstrual bleeding national audit questionnaire,\textsuperscript{111} and v) the VEINES symptom questionnaire.\textsuperscript{112} The health questionnaire also included visual analogue scores (VAS) to measure the severity of pain.

Current health status was assessed using EuroQol (EQ-5D-3L).\textsuperscript{113} The EQ-5D-3L system is a generic, multi-attribute, preference-based measure made up of five three-level domains: mobility, pain/discomfort, self-care, usual activities, and anxiety. Use of healthcare resources (e.g. visits to healthcare professionals, inpatient or Accident and Emergency visits) and out-of-pocket costs (e.g. over the counter medicine) over the previous 12 months was also reported with the clinic visit that triggered recruitment excluded.
Statistical analysis

Statistical analysis was conducted using SPSS® versions 20 (SPSS®, Chicago, USA). The non-normally distributed VAS severity scores were compared between the groups using chi-squared and chi-squared with Bonferroni correction. Categorical data was analysed using chi-squared test and continuous data with ANOVA, followed by Scheffe’s tests or Kruskal-Wallis tests with Bonferonni-adjusted Mann-Whitney U-tests as appropriate. The conventional 5% significance level was used. Published UK social preference weightings were used to transform EQ-5D-3L scores into a measure of health-related quality of life (HR-QoL). Cases were matched for age and parity with controls retrospectively.

Results

In total 70 women (35 cases and 35 controls) were recruited from gynaecology clinics in two UK hospitals.

Comparability of groups

Both cases and controls were matched for age and parity retrospectively. Mean age (range) was 34.5 (22-47) for the CPP cases compared with 34.5 (19-52) for the healthy controls (table 13). Gravida and parity were similar in both groups with median (range) parity of 1 (0-4) in CPP cases compared with 1 (0-4) in healthy controls. BMI was similar in both groups at 24.1 (19-39) in CPP cases and 23.7 (18-36) in healthy controls. Smoking history was similar in the two groups.
Table 13 Cases and matched control comparability

<table>
<thead>
<tr>
<th></th>
<th>CPP cases (n=35)</th>
<th>Healthy controls (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age</td>
<td>34.5 (22-47)</td>
<td>34.5 (19-52)</td>
<td>-</td>
</tr>
<tr>
<td>95% CI</td>
<td>31.7, 37.2</td>
<td>31.4, 37.6</td>
<td></td>
</tr>
<tr>
<td>Median (range) gravida</td>
<td>2 (0-6)</td>
<td>2 (0-5)</td>
<td>p=0.231*</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.3</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Median (range) parity</td>
<td>1 (0-4)</td>
<td>1 (0-4)</td>
<td>p=0.442*</td>
</tr>
<tr>
<td>95% CI</td>
<td>1,2</td>
<td>0,2</td>
<td></td>
</tr>
<tr>
<td>Mean (range) BMI</td>
<td>24.1 (19-39)</td>
<td>23.7 (18-36)</td>
<td>p=0.74*</td>
</tr>
<tr>
<td>95% CI</td>
<td>22.7, 25.5</td>
<td>22.2, 25.2</td>
<td></td>
</tr>
<tr>
<td>Smoking (n,%)</td>
<td>7 (20%)</td>
<td>6 (17%)</td>
<td>p=1.0*</td>
</tr>
<tr>
<td>95% CI</td>
<td>10%, 36%</td>
<td>8%, 33%</td>
<td></td>
</tr>
</tbody>
</table>

* two-tail sample t-test; # Chi-squared test

Frequency of pelvic vein incompetence

All 70 women underwent trans-vaginal ultrasound to identify PVI. Within the case group 16 of 35 (46%) demonstrated PVI on ultrasound compared with 7 of 35 (20%) of healthy controls (p=0.02, chi-squared test). Odds ratio (OR) of 3.37 (1.16 to 9.74; 95% CI). Cumulatively, left ovarian vein was incompetent in 10 of 70 (14%), right ovarian vein incompetence in 9 of 70 (13%), left internal iliac incompetence in 12 of 70 (17%) and right internal incompetence in 7 of 70 (10%).
Health status

Women with CPP had a median (range) EQ-5D-3L utility score of 0.8 (-0.75-1.0) compared with 1.0 (0.41-1.0) for healthy controls (p<0.001, Kruskal-Wallis test). The EQ-5D-Visual analogue sore (VAS) had a median (range) score of 74.2 (25-100) for CPP cases compared with 86.2 (50-100) for healthy controls (p=0.003, ANOVA test). Pain was the primary limiting factor in quality of life for the CPP cases.

When comparing women with CPP and PVI (n=16) with women with CPP only (n=19), no statistical difference was identified in utility score 0.78 (-0.08-1.0) compared with 0.8 (0.62-1.0, p=0.59).

Symptom history

As expected, all 35 of 35 (100%) CPP cases stated they experience CPP compared with 12 of 35 (34%) healthy controls. CPP cases experienced pain associated with periods and sexual intercourse (table 14). Comparing women with CPP and PVI (n=16) with women with CPP only (n=19) no significant difference was seen in the nature of pain symptoms or how it was described.
# Table 14 Descriptions of pain reported by participants

<table>
<thead>
<tr>
<th>Pain Description</th>
<th>Cases (n=35)</th>
<th>Healthy controls (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain before periods VAS (median, range)</td>
<td>35 (100%) 50 (15-100)</td>
<td>8 (23%) 0 (0-60)</td>
</tr>
<tr>
<td>Pain during periods VAS (median, range)</td>
<td>35 (100%) 50 (10-100)</td>
<td>11 (31%) 0 (0-80)</td>
</tr>
<tr>
<td>Pain throughout month VAS (median, range)</td>
<td>29 (83%) 25 (0-100)</td>
<td>5 (14%) 0 (0-50)</td>
</tr>
<tr>
<td>Pain during sex VAS (median, range)</td>
<td>20 (57%) 25 (0-75)</td>
<td>3 (9%) 0 (0-75)</td>
</tr>
<tr>
<td>Pain opening bowels VAS (median, range)</td>
<td>22 (63%) 0 (0-75)</td>
<td>2 (6%) 0 (0-25)</td>
</tr>
<tr>
<td>Lower back pain VAS (median, range)</td>
<td>35 (91%) 50 (0-100)</td>
<td>6 (17%) 0 (0-75)</td>
</tr>
<tr>
<td>Feeling bloated VAS (median, range)</td>
<td>31 (89%) 50 (0-100)</td>
<td>9 (26%) 0 (0-100)</td>
</tr>
</tbody>
</table>
Discussion

This chapter illustrates that when matched for age and parity, women with CPP have a higher frequency of PVI when compared with healthy controls (46% vs. 20%; OR 3.37, p=0.02).

When comparing health status and pain symptoms, no significant difference could be determined between women with CPP and PVI compared with women with CPP only. It is unclear of the significance of this as women in both groups predominantly scored ‘pain’ or ‘anxiety’ as the factor reducing health status. In order to determine a statistical significance a larger sample size would be required, or a more sensitive anxiety specific health tool could be used such as the Generalised Anxiety Disorder 7-item tool (GAD-7) or the Patient Health Questionnaire (PHQ-9). Should there still be no significance between the two groups of women with CPP (with and without PVI) that would indicate PVI actually may not impact health status or pain symptoms. However women in the CPP group did report a lower health status compared with the healthy controls highlighting the disease burden CPP represents.

The results of this study support prior research which highlights a strong association between CPP and PVI. The frequency of PVI in women with and without CPP identified through this study mirrors the results of previous observational studies which showed PVI to be present in 30% of women with CPP compared with 9% of healthy women shown in a further study.7276

The strength of this study is its robust design and matching the cases and controls for both age and parity. All women underwent the same TVU protocol performed by one of two-trained vascular technologist. A limitation of this study is the relatively small sample size which although was large enough to determine a significant difference in prevalence, was not large enough to determine a difference in health status and pain symptoms. Additional tools such as GAD7 could be used to determine anxiety and psychological impact of PVI, however this would increase patient burden and could lead to an increased dropout rate.
Based on previous literature and this study, we can assume the prevalence of PVI in healthy women with no CPP is between 10-20%. Our PPI group and women’s health experts advised that the prevalence of PVI in women with CPP would need to be at least double the prevalence in controls (i.e. 10 v. 20%) to be deemed clinically important. To detect such a difference with 80% power, we would require 225 case-control pairs (based on a simple McNemar’s test with an estimated discordant proportion based on the independence assumption of 0.24, using the conventional 5% significance level). Based on the Hills Criteria for causation, it is felt that the relationship between PVI and CPP meets the minimum conditions needed to present causation. Although we cannot show a temporal relationship, we have demonstrated a strong association and a plausible and consistent argument. It is however difficult to determine the dose-response as pain-coping mechanism are so different.

This study is currently in-progress with recruitment continuing to the intended target of 225 case-control pairs. This is the first adequately powered study determining the relationship between PVI and CPP. Identifying a causal relationship would lead to focused diagnostic pathways and a reduced need for invasive surgical procedures. Understanding the impact on health-related quality of life and use of healthcare provides a basis for future studies evaluating potential treatments for PVI. Showing no relationship between PVI and CPP would prevent women undergoing unnecessary procedures commonly used to treat PVI. We hope to reduce the suffering of women with CPP.

**Chapter summary**

This study shows that PVI is more prevalent in women with CPP than healthy women, suggesting a strong association with CPP. Although association does not imply causation, further research into PVI as a cause of CPP is warranted. Demonstrating that removing PVI (occluding incompetent pelvic veins) improves CPP symptoms would establish a causal relationship. The sample described in this study is underpowered to determine a significant difference in health-related quality of life and symptom profile between women with CPP and PVI compared
with women with CPP only but recruitment is ongoing and intended to recruit to a target of 225 case-control pairs.
CHAPTER 8: TRANS-VENOUS OCCLUSION OF INCOMPETENT PELVIC VEINS FOR CHRONIC PELVIC PAIN IN WOMEN: A SYSTEMATIC REVIEW

This manuscript has been published in the European Journal of Obstetrics and Gynaecology EJOG 2015; 185 156–163. 10.1016/j.ejogrb.2014.12.011

Abstract

Background: Chronic pelvic pain (CPP) affects 24% of women worldwide; the cause cannot be identified in 40% despite invasive investigations. Dilated, refluxing pelvic veins may be a cause of CPP and treatment by trans-venous occlusion is increasingly performed when gynaecological causes are excluded, but is it effective?

Methods: A systematic review of the literature published between 1966 and July 2014 was conducted. Two authors independently reviewed potential studies according to a set of eligibility criteria, with a third assessor available as an arbiter.

Results: Thirteen studies including 866 women undergoing trans-venous occlusion of pelvic veins for CPP were identified (Level of evidence: one study grade 2b, 12 studies grade four). Statistical significant improvements in pelvic pain were reported in nine of the 13 studies. Technical success was reported in 865 of 866 (99.8%) with low complication rates: coil migration in 14 women (1.6%), abdominal pain in ten women (1.2%) and vein perforation in five (0.6%). In a study on varicose veins of the legs, recurrence was seen in 13% of 179 women 5-years following coil embolisation.

Conclusion: Subjective improvements in pain were seen in all 13 studies after treatment by trans-venous occlusion. All 13 studies were of poor methodological quality. Complication rates were low and no fatalities occurred. Well-designed studies are essential to determine whether pelvic vein incompetence (PVI) is associated with CPP, and to explore whether trans-venous occlusion of PVI improves quality of life for these women.
Introduction

Chronic pelvic pain (CPP) is defined as continuous or intermittent lower abdominal or pelvic pain of at least six months duration.1 It is a major health problem with a worldwide prevalence of 24% and accounting for 20% of all gynaecology outpatient appointments in the UK.128 Primarily affecting young women, CPP is associated with significant mental, social and physical burden for sufferers, leading to reduced quality of life, loss of employment, marital discord and greater use of healthcare resources.2 39 Its management has remained a challenge for healthcare professionals, with nearly 55% of women with CPP having no obvious cause for their pain on laparoscopy.2 8

Pelvic vein incompetence (PVI) is thought to be a possible cause for CPP. Despite being thought to affect 15-20% of women, remarkably we know very little about it and it is rarely diagnosed in the United Kingdom.46 74 Taylor in 1949 first described how incompetent and distended pelvic veins might cause symptoms of pain, dyspareunia and menstrual dysfunction.55 58 133 Since then, despite being frequently reported to be a cause for CPP in published literature, there have been no adequate studies on the frequency of PVI in women with CPP. It is often missed on laparoscopy as the distended pelvic veins empty when the patients are tilted head down.

Treatments suggested for PVI include total abdominal hysterectomy, pelvic vein ligation or occlusion, and hormonal therapy.102 Medroxyprogesterone acetate (MPA) has been shown to temporarily improve pain scores but was associated with side effects including weight gain and acne.134 Pelvic vein ligation is now rarely performed and total abdominal hysterectomy is unacceptable to younger women.

Trans-venous occlusion of pelvic veins using percutaneous cannulation of a jugular or femoral vein and insertion of coils and sclerosants into the incompetent vein, leads to permanent occlusion by thrombosis. Despite the absence of any adequate randomised control trial (RCT) on the effectiveness of trans-venous occlusion, it is
becoming increasingly performed in the private sector and throughout Europe, at considerable cost to sufferers.

The primary aim of this systematic review was to review and critically appraise the evidence available regarding trans-venous occlusion in the treatment of CPP in women. The primary outcome measure reviewed was clinical effectiveness and safety.

Methods

Types of studies
We included published randomised controlled trials (RCT), quasi-control trials, cohort studies, and case-control studies. We excluded unpublished studies or those including less than 15 participants. Review articles, editorials, letters, and case reports were also excluded.

Types of participants
Women with CPP, defined as continuous or intermittent lower abdominal or pelvic pain lasting for more than six months (not occurring exclusively with menstruation, intercourse or pregnancy) and with pelvic congestion symptom, defined as CPP thought to be caused by PVI, were included. We excluded studies examining specific cohorts of women known to have solely endometriosis, primary dysmenorrhoea or chronic pelvic inflammatory disease.

We also excluded any study in which the diagnosis of PVI has not been confirmed by imaging such as reflux venography, trans-vaginal ultrasound, and CT or MR venography.
Types of interventions

Studies on trans-venous occlusion using metallic coils or foam/gel sclerotherapy were included.

Search methods for study identification

We searched all published studies to 8 June 2014 with no language restriction. Several large electronic searches were conducted on the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, MEDION, SIGLE, LILACS, PsycINFO, Index of scientific and technical proceedings, DARE, and the British Nursing Index.

The search consisted of a combination of MeSH or keywords (chronic pelvic pain, pelvic congestion syndrome (PCS), pelvic vein incompetence) combined using 'and' with MeSH or keywords for intervention (embolisation, venous occlusion, sclerotherapy). The search strategy adopted is shown in Appendix 3. The reference lists of relevant publications and review articles were searched. We hand searched relevant journals, abstracts and conference proceedings and several grey literature sources.

Selection of studies

Two authors independently reviewed potential studies for compliance with the inclusion criteria. A third assessor was available as an arbiter when there was uncertainty regarding eligibility. The selection process is shown in table 16.

Data extraction and management

A data extraction form designed and piloted by the review authors was used by the two authors independently to identify variables and potential biases in the eligible studies. Disagreements or uncertainty was settled by discussion with a third author. In particular, the following was identified: Study design (prospective,
retrospective, randomised), patient demographics (age, ethnicity, socioeconomic status), eligibility criteria for patients, vein occlusion technique, length of follow up and outcome measures (pain scores, quality of life, technical success and adverse outcomes). The systematic review followed quality reporting guidelines set by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).135

**Study evaluation and critical appraisal of the evidence**

Analysis of the evidence presented in selected studies was performed using the Critical Appraisal Skills Programme (CASP).136 137 The CASP tool consists of 12 questions which consider: study validity, risk of bias in recruitment, exposure, outcome measurement, confounding factors, reporting of results and the transferability of findings. Each question can be answered with “yes”=2, “can’t tell” =1, and “no”=0. The questions “what are the results of this study?” and “what are the implications of this study for practice?” were not included for each individual study as these questions cannot have graded answers. Each study was graded independently by two review authors. Disagreements were resolved by discussion.

Level of evidence was determined using the Oxford Centre of Evidence-based Medicine (CEBM) Levels of Evidence (March 2009).138

**Assessment of heterogeneity**

We considered the clinical and methodological characteristics of the included studies to decide whether they were sufficiently similar for meta-analysis to provide a clinically meaningful summary. If substantial heterogeneity was determined, the authors planned to reassess the data and perform a narrative review.
Results

Results of the search
A total of 3,456 study titles were identified by the initial search strategy. Of these, 1,966 studies were excluded after title searching. A total of 232 relevant abstracts were reviewed and 26 papers were selected for further review of full-text publications (figure 19).

Of these 26 eligible full-text publications, 13 were excluded for one or more of the following reasons: less than 15 subjects (Bachar, Tarazov), the study focused on the treatment for varicose veins (Monedero, Ratnam, Tinelli), assessed hormone therapy in women with pelvic congestion syndrome (Soysal, Simsek, Shokeir, Farquhar, Reginald), assessing surgery in women with pelvic congestion syndrome (Beard), or only the abstract was available (Morgan, Machan) leaving 13 studies (table 15).

Included studies
Of the 13 studies evaluating pelvic vein occlusion in women suffering from CPP or pelvic congestion syndrome, Ten studies were prospective and two retrospective. Only one was a quasi-randomised trial with no untreated controls. Seven studies had no pre-determined follow up interval with participants followed up at variable times. Overall patient follow-up ranged from one to five years.

All 13 studies were from single centres, with three studies conducted in the USA, three in Belgium, two in Italy and Korea, and one each in Germany, France and Spain.

Quality of evidence
The CASP tool for observational studies and RCTs was used to appraise the presented evidence. The only quasi-randomised trial compared coil embolisation with hysterectomy plus uni or bilateral oophorectomy and had no untreated controls. Even
this study failed to describe the randomisation process, attempt to ‘blind’ outcome assessments, or document loss to follow up.\textsuperscript{105}

The level of evidence was assessed using Oxford CEBM guidance. The only RCT was graded as level 2b, with the remaining 12 studies graded as level 4. In view of the highly heterogeneous results, pooled success estimates through meta-analysis was not possible or deemed appropriate, as any data synthesis of these results would be likely to provide misleading conclusions about the effectiveness of trans-venous occlusion.

**Participants**

Trans-venous occlusion was performed in 866 women with CPP, pelvic congestion syndrome or pelvic pain which was not clearly defined. The mean ages in the studies varied between 32 to 49 years, with mean gravida ranging between 1 and 3.1.

Recruitment was from gynaecology, vascular surgery and varicose vein clinics with the number of patients ranging from 19-179. In three studies, varicose veins were treated after trans-venous occlusion of PVI.\textsuperscript{150,151,152} Treatment for varicose veins ranged from sapheno-femoral disconnection with stripping of the great saphenous vein, redo surgery at the sapheno-femoral junction or phlebectomy, depending on the distribution of varices.

Explicit criteria for diagnosis of CPP or pelvic congestion syndrome were rarely specified, and terminology describing the participant’s condition varied widely. Participants were commonly labelled as suffering from ‘chronic pelvic pain’ ‘pelvic congestion syndrome’ or ‘pelvic vein syndrome’ without specifying the criteria or chronicity of symptoms. Seven studies did not record whether a gynaecologist was involved in making the diagnosis of CPP or pelvic congestion syndrome. Only one study, a quasi-randomised trial, undertook diagnostic laparoscopy in all participants before inclusion.\textsuperscript{105} Trans-vaginal ultrasound was the only pelvic investigation in another study.\textsuperscript{151} Two studies undertook no investigations for alternative causes of pelvic pain before performing coil embolization of ‘incompetent’ pelvic veins.\textsuperscript{150,152} The remaining studies did investigate for alternative causes, but investigations varied, and not all participants were subjected to the same assessments within the study.
Intervention

Trans-venous occlusion of ovarian and internal iliac veins was performed in 866 women via femoral or jugular vein trans-catheter insertion of metallic coils, sclerosants or glue. Seven studies only investigated women for ovarian vein incompetence, with the remaining studies including both ovarian and internal iliac vein incompetence. Two studies used sodium tetradecyl-sulfate foam sclerotherapy only, while the remaining 11 used either metallic coils alone or in combination with foam sclerotherapy.

Technical success and complication rates

The technical success of occluding incompetent ovarian or internal iliac veins, defined as completely occluding a vein that previously showed reflux, was high in all the studies (98% to 100%). Failure to occlude a right ovarian vein due to vasospasm was described in one case. Ten studies described the technique used for trans-venous occlusion in sufficient detail to allow replication. The procedure was performed via femoral or jugular vein catheterisation under local anaesthetic or sedation in all studies.

The procedure was reported to be safe with complications in only 29 (3.3%) patients. Complications reported included 5 (0.6%) perforations or injuries to the target vein, coil migration into the pulmonary artery in 12 (1.4%) patients or renal circulation in 2 (0.2%). Migrating coils were all snared (except one case in which the patient refused coil recovery) with no clinical consequences. Abdominal pain occurred in 10 (1.2%) women. Abdominal pain was usually transient and occurred during the procedure and settled with simple analgesics. No long term complications or deaths were reported in any of these studies.

Outcome measures

There was no agreement on how to report outcomes. Eight studies used visual analogue scales for pain, two used a combination of visual analogue score and a pain questionnaire. One measured the impact of coil embolisation on the menstrual cycle intervals and length. Kim et al assessed the impact of coil embolisation on
hormonal levels on the third day of the menstrual cycle. Health-related quality of life and health care utilisation was not explored in any of these studies.

Effects of intervention

Vein diameter was determined before and after trans-venous occlusion using trans-vaginal ultrasound at rest and during Valsalva manoeuvre in one study. The mean diameter of the right ovarian vein reduced from 4.5mm to 3.19mm, whilst the left ovarian vein reduced from 6.3mm to 4.5mm six months after foam sclerotherapy. Complete thrombosis of the utero-ovarian varices was demonstrated by trans-abdominal ultrasound in 13 of 19 (68.4%) of women, while partial occlusion was noted in 2 of 19 (10.5%) after embolisation. No significant difference was determined between the success rates and the occlusion material used.

All thirteen studies reported subjective improvements in pain symptoms after occlusion of incompetent ovarian or internal iliac veins. Improvements were seen in pelvic pain frequency, dysmenorrhea and dyspareunia lasting up to 5-years in some studies. Five studies reported on symptom recurrence; this ranged from 4-17% over a 12 month to 5-year interval. Four successful pregnancies were reported after trans-venous occlusion of PVI. In a study on coil embolization in 179 women with varicose veins, there was recurrence of varicose veins in 24 (13%) by 5-years. Patient acceptability or satisfaction with the procedure was not reported in any of the 13 studies.
<table>
<thead>
<tr>
<th>Author, date, country</th>
<th>Patient group</th>
<th>Treatment</th>
<th>Study type</th>
<th>Outcomes, follow up period</th>
<th>Key results</th>
<th>CASP grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asciutto et al. 2009</strong>&lt;br&gt;Germany 150</td>
<td>71 women with history of pelvic or menstrual discomfort</td>
<td>Ovarian (OV) and internal iliac (IIV) vein coil embolisation</td>
<td>Prospective observational study</td>
<td>Pain questionnaire Visual analogue scale (VAS) 3 year follow up</td>
<td>Significant improvement of symptoms after embolisation in patients with isolated OV incompetence. Mean 5.2 SD 3.5 before and 1.2 SD 0.9 after treatment; p&lt;0.0001.</td>
<td>17</td>
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<tr>
<td><strong>Capasso et al. 1997</strong>&lt;br&gt;Belgium 157</td>
<td>19 women with PCS</td>
<td>Bilateral ovarian vein glue/coil embolisation</td>
<td>Prospective observational study</td>
<td>Pain score Trans-abdominal ultrasound 15 month follow up</td>
<td>74% of patients had improvements in pain symptoms (complete relief in 58%, partial in 16%). 26% had persistent dyspareunia. Complete thrombosis in 72.2%, partial occlusion in 11.1%. Unchanged in 16.7%.</td>
<td>9</td>
</tr>
<tr>
<td><strong>Chung et al. 2003</strong>&lt;br&gt;Korea105</td>
<td>106 women with PCS</td>
<td>a) Unilateral ovarian vein embolisation</td>
<td>Quasi-randomised trial</td>
<td>Visual analogue scale</td>
<td>Mean VAS from 7.8 to 3.2 for embolisation (P&lt;0.05), vs.</td>
<td>9</td>
</tr>
<tr>
<td>Study Reference</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Procedures</td>
<td>Follow-up</td>
<td>Outcome Measures</td>
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<tr>
<td>Creton et al. 2007 France 152</td>
<td>24 women with pelvic vein syndrome</td>
<td>Ovarian and internal iliac vein coil embolisation</td>
<td>Prospective observational study</td>
<td>3 year follow up</td>
<td>Mean clinical improvement score was 80%, 77%, 80% and 76% respectively at 45 days, 1, 2, 3 years.</td>
<td></td>
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<tr>
<td>D'Archambeau et al. 2004 Belgium 149</td>
<td>48 women with PCS</td>
<td>Bilateral ovarian vein coil and/or glue embolisation</td>
<td>Retrospective observational study</td>
<td>Mean follow up 43 months</td>
<td>Mean VAS improved from 7.9 to 2.2 (p&lt;0.001)</td>
<td></td>
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<tr>
<td>Gandini et al. 2007 Italy 148</td>
<td>38 women with CPP</td>
<td>Ovarian vein foam sclerotherapy (3% STSF)</td>
<td>Retrospective observational study</td>
<td>12 months follow up</td>
<td>VAS 7.8 to 2.7 pelvic pain, 4.9 to 2.2 menstrual pain and similar for urinary urgency and</td>
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</table>

b) Hysterectomy with bilateral oophorectomy (n=27)
c) Hysterectomy with unilateral oophorectomy (n=27)
<table>
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<tr>
<th>Study</th>
<th>Country</th>
<th>Sample Size</th>
<th>Inclusion Criteria</th>
<th>Study Design</th>
<th>Pain Measure</th>
<th>Follow Up</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Kwon et al. 2006</td>
<td>Korea</td>
<td>67 women</td>
<td>Bilateral ovarian vein coil embolisation</td>
<td>Prospective observational study</td>
<td>Pain severity scale</td>
<td>Mean follow up 45 months</td>
<td>82% experienced pain reduction after coil embolisation. 12 patients reported no change in pain levels or had become more severe.</td>
</tr>
<tr>
<td>Kim et al. 2006</td>
<td>USA</td>
<td>127 women</td>
<td>Bilateral ovarian vein coil/sclerosant embolization with interval IIV embolisation</td>
<td>Prospective observational study</td>
<td>Visual analogue scale</td>
<td>Mean follow up 45 months</td>
<td>Mean pelvic pain had improved significantly from $7.6 \pm 1.8$ before embolisation to $2.9 \pm 2.8$ after embolisation ($P &lt; 0.0001$). 83% exhibited clinical improvement at long-term follow-up.</td>
</tr>
<tr>
<td>Laborda et al. 2013</td>
<td>Spain</td>
<td>179 women</td>
<td>Bilateral ovarian vein embolisation</td>
<td>Prospective observational study</td>
<td>Visual analogue scale</td>
<td>5 year follow up</td>
<td>Complete disappearance of symptoms in 60 patients (33.5%). VAS was $7.34 \pm 0.7$ pre-procedural versus $0.78 \pm 1.2$ at 5 years. ($p &lt; 0.0001$).</td>
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<tr>
<td>Publication</td>
<td>Country</td>
<td>Study Design</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>Outcome</td>
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<td>Maleux et al, 2000</td>
<td>Belgium</td>
<td>Prospective observational study</td>
<td>Bilateral ovarian vein glue/coil embolization</td>
<td>Mean follow up 20 months.</td>
<td>59% total relief, 10% with some relief</td>
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<tr>
<td>Pieri et al. 2003</td>
<td>Italy</td>
<td>Prospective observational study</td>
<td>Bilateral ovarian vein foam sclerotherapy (3% STSF)</td>
<td>Pain scale</td>
<td>Mean vessel diameter reduced from 4.5mm to 3.19mm of the right OV and 6.3mm to 4.5mm of the left OV. CPP was present in only 39% of patients after 1 month.</td>
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<tr>
<td>Scultetus et al. 2002</td>
<td>USA</td>
<td>Prospective observational study</td>
<td>1A: vulval varices sclerotherapy (n=5) 1B: gonadal vein excision and sclerotherapy (n=10) 2A: Gonadal vein resection (n=12) 2B: Gonadal vein</td>
<td>Visual analogue scale</td>
<td>1A + 1B; 12 patients had excellent results and three had moderate results. 2B: 3 patients treated with GVE were asymptomatic.</td>
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<tr>
<td>Venbrux et al. 2002 USA</td>
<td>56 women with CPP</td>
<td>Ovarian and internal iliac vein coil embolisation</td>
<td>Prospective observational study</td>
<td>Visual analogue scale, Menstrual cycle questionnaire</td>
<td>Mean baseline pain level was 7.8 (n=56); at 3-month follow-up 4.2 (n=56); at 6 months 3.8 (n=41); at 12 months 2.7 (n=32) (P&lt;0.001).</td>
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<tr>
<td>embolization (GVE) (n=7)</td>
<td>3A: Hypogastric vein division (n=5)</td>
<td>3B: Hypogastric vein embolization (HVE) (n=6)</td>
<td>3C: Hypogastric vein embolisation + gonadal vein resection (n=12)</td>
<td>3B: Five patients treated with HVE were asymptomatic, and one had no improvement.</td>
<td>3C: 10 were asymptomatic.</td>
<td>15</td>
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</table>

Venbrux et al. 2002
USA

56 women with CPP

Ovarian and internal iliac vein coil embolisation

Prospective observational study

Visual analogue scale, Menstrual cycle questionnaire

Mean baseline pain level was 7.8 (n=56); at 3-month follow-up 4.2 (n=56); at 6 months 3.8 (n=41); at 12 months 2.7 (n=32) (P<0.001).
Figure 19 Flow diagram of search results

Titles identified through database searching
\[ n = 3456 \]

Titles screened after removal of duplicates
\[ n = 2198 \]

Titles excluded
\[ n = 1966 \]

Abstracts screened
\[ n = 232 \]

Full text articles assessed for eligibility
\[ n = 26 \]

Excluded (\( n = 13 \)):
- 2 studies less than 15 subjects
- 3 studies primary outcome varicose vein reoccurrence
- 5 studies assessing hormone therapy
- 1 study assessing surgery
- 2 studies had only the abstract available

72 Duplicates
7 reviews
8 comment letters
18 case reports
1 abstract only
97 papers not relevant to topic

13 studies included in this systematic review
Discussion

This review identified 13 studies assessing trans-venous occlusion as a treatment in women with CPP or pelvic congestion syndrome. Trans-venous occlusion can be performed as a day-case procedure under local anaesthesia usually without sedation. All 13 studies reported improved subjective pain symptoms assessed by a variety of outcome measures after treatment. Trans-venous occlusion was also shown to be safe with good technical success in over 98% of women. The most serious complication was that of migration of the coil into the lungs which did not lead to any further clinical consequences. No differences were identified between the occlusion agents used. Neither acceptability of the procedure to women, or its impact on health-related quality of life was reported in any of these studies.

The strength of this review is the extensive literature search performed in relevant databases. Two independent authors screened and identified relevant studies, with a third author being available to settle disagreements. A weakness of this review is the quality of the available published studies. Study design was the major limiting factor in the 13 studies which were all liable to observer bias as there were no or inappropriate controls (Level of evidence: one study grade 2b, 12 studies grade four).

This review highlights the poor quality of research in this area. A well-designed RCT is urgently needed to assess trans-venous occlusion in an unbiased fashion to definitively determine whether there is a causal relationship between PVI and CPP. After review of the current literature, we would suggest the recruitment of women with confirmed CPP by a gynaecologist. Where possible, it is important to rule out the presence of alternative pathologies (such as endometriosis) before patients are selected for treatment in a RCT to avoid potential confounding factors. Multi-centred recruitment would help to provide the required number of participants who have had all other causes for their pain excluded.

Future studies would also benefit from using disease specific outcome measures and quality of life scores such as the Euroqol (EQ-5D) or SF-36 to determine the impact of the intervention. Several studies used the visual analogue scale which has been shown to be very effective and responsive in determining the impact of a treatment in chronic
conditions. The addition of scores such as the Short-Form McGill Questionnaire may assist in determining the impact of treatment and are recommended for use by the International Pelvic Pain Society. Follow up protocols need to be more robust. We suggest immediate follow up (1-2 weeks) followed by longer follow up (6months-5 years) as in our experience patients do describe almost immediate changes to their pain symptoms after intervention.

Chapter summary

This systematic review reports on 13 studies evaluating trans-venous occlusion of incompetent pelvic veins in women with CPP and pelvic congestion syndrome. All included studies reported improvements in the frequency and severity of pelvic pain symptoms after treatment. However, all 13 studies were of poor methodological design with significant bias that limited the value of the evidence to healthcare planning.

Technical success in terms of the initial occlusion of target veins was high (98-100%) with few and minor complications. There were no deaths or serious morbidity. The impact on quality of life was not assessed in any of the included studies.

Well-designed epidemiological studies are urgently needed to establish the frequency of PVI in women with CPP. Well-designed RCTs are required to truly establish the impact of trans-venous occlusion of incompetent pelvic veins on symptoms in women with CPP.
CHAPTER 9: TRANS-VENOUS OCCLUSION OF INCOMPETENT PELVIC VEINS AS A TREATMENT FOR CHRONIC PELVIC PAIN IN WOMEN: A RANDOMISED CONTROLLED TRIAL

This protocol is published on the ISRCTN Registry, BioMed Central. DOI 10.1186/ISRCTN15091500 (access: http://www.isrctn.com/ISRCTN15091500)

Abstract

Pain in the lower abdomen or pelvis for more than six months is known as chronic pelvic pain (CPP). CPP affects millions of women worldwide and accounts for 20-40% of all gynaecology outpatient appointments in the UK. Pelvic vein incompetence (PVI), where the valves within the pelvic veins fail as they do in varicose veins affects 15-20% of women and may cause CPP. Remarkably, we know little about PVI as the distended veins empty when women are tilted head down during laparoscopy, the usual investigation for CPP.

The effectiveness of blocking the incompetent pelvic veins with small coils was reported in 13 studies which were all of poor quality with bias. As a result, The Royal College of Obstetrics and Gynaecology (RCOG), The National Institute of Clinical Excellence (NICE) and NHS are understandably reluctant to support treatment for PVI even though all of these studies report that women benefited from treatment. The male equivalent, varicoceles caused by testicular vein incompetence, are treated by the NHS.

Blocking incompetent pelvic veins with coils in women with PVI has never been tested in a well-designed clinical trial. We plan to recruit 100 women with CPP and PVI confirmed by trans-vaginal ultrasound from three women’s health centres in the North West. Patients will be selected for trans-venous occlusion or best standard treatment at random to produce two equal groups. All participating
women will complete detailed questionnaires on how the treatment has impacted their symptoms, quality of life and NHS costs of care.

This study will report whether symptoms suffered by these women are improved by this treatment. We will also be able to report on changes in quality of life and NHS costs.
Introduction

Defined as continuous or intermittent lower abdominal or pelvic pain of at least six months duration (not occurring exclusively with menstruation, intercourse or pregnancy), chronic pelvic pain (CPP) is widely accepted to be a major health problem with a worldwide prevalence in women of 24%.\(^1\)\(^4\) CPP primarily affects younger women, and is a leading cause of impaired quality of life, causing disruption to their daily life, social isolation, relationship difficulties and loss of work-related productivity.\(^2\)\(^10\) Over 18% of employed women take time off work due to CPP.\(^4\) Over 40% of women fail to achieve a diagnosis, with many discouraged and disengaged from the healthcare service despite continuing symptoms.\(^39\)

The economic burden of CPP is difficult to establish as there are no recent data. Annual treatment costs in the UK were estimated to be £182 million/year in 1992.\(^2\) The reported costs of managing CPP in the USA was estimated at $100 billion/year in 1998.\(^160\) Approximately 38 per 1000 women attend primary care with CPP each year in the UK, a rate comparable with migraine, asthma and back pain.\(^4\)\(^161\) They are usually referred to a gynaecologist (accounting for 20-40% of gynaecology all referrals in the UK) and undergo repeated hospital admissions with invasive investigations such as diagnostic laparoscopy or even hysterectomy.\(^64\)\(^162\) The emotional distress from these invasive treatments is substantial.

Pelvic vein incompetence (PVI) where the valves in the pelvic veins fail in the same way as they do in varicose veins, affects 15-20% of all women and yet we know little about it as the pelvic veins are emptied when women are tilted head-down to clear the gut from the pelvis during laparoscopy. There is increasing evidence that PVI may be an important cause of CPP.\(^60\)\(^102\)

We undertook a case-control study funded by the Collaboration for Leadership in Applied Health Research and Care (CLAHRC) to explore the symptoms experienced by women with PVI. Mean age (range) was 39.8 (24-47) years for cases, 39.1 (24-49) for varicose vein controls and 38 (25-49) for healthy controls. Pelvic pain was
reported by 38 of 40 (95%) PVI cases, compared with 25 of 40 (62%) varicose vein controls, and 26 of 40 (65%) healthy controls (p=0.001). The median (range) EQ-5D utility score for PVI cases was 0.80 (0.29-1.0) compared with 0.80 (0.09-1.0) for varicose vein controls and 1.0 (0.62-1.0) for healthy controls (p=0.002). Of the 40 PVI cases, 35 (88%) visited a consultant in the previous 12 months compared with 12 of 40 (30%) varicose vein controls, and 14 of 40 (35%) healthy controls (p<0.001). NHS costs were significantly higher in our PVI cases then in their two control groups. This study supports the growing evidence on a relationship between PVI and CPP.

Our systematic review of the literature published between 1966 and July 2013 revealed 13 studies evaluating the influence of trans-venous occlusion of PVI in 866 women with CPP. Twelve studies were retrospective and one quasi-randomised trial (level of evidence: graded 4 and 1b respectively). Statistically significant improvements in pelvic pain were reported in nine of the 13 studies, with one study reporting mean pain levels improvement from 7.6±1.8 before occlusion to 2.9±2.8 after treatment in 108 women with PVI and CPP (p < 0.0001). The only quasi-randomised trial compared coil occlusion with hysterectomy but had no untreated controls. Trans-venous occlusion was significantly more effective at reducing pelvic pain than hysterectomy (p<0.05). However this study failed to describe the randomisation process and there was no attempt to 'blind' the outcome assessment.120

Data on loss to follow up was not reported in any of these 13 studies. Overall, technical success was reported in 865 of 866 (99.8%) procedures with few complications: coil migration occurred in 14 women (1.6%), and abdominal pain in ten women (1.2%).120 Due to the poor quality of this evidence, treatment for PVI is not available on the NHS and there is no guidance on its management from RCOG or NICE. The male equivalent, varicoceles caused by testicular vein incompetence, is treated on the NHS.

It is important and timely that the clinical and cost-effectiveness of pelvic vein occlusion be assessed in a pragmatic RCT. Research in CPP was recently prioritised
by the NIHR, and trans-venous treatments have become routine in the treatment of vascular disease. Patients with CPP with no diagnosis may be investigated for PVI using a minimally invasive trans-vaginal approach. It will allow clinicians to focus their investigations, reducing the need for recurrent and often prolonged admissions required for invasive investigations. It will assist the RCOG and NICE in the development of evidence-based guidance on the management of PVI in women with CPP. Our planned economic analysis will guide future research on whether treatment by coil occlusion will be cost-effective and will inform the economic analyses required for a definitive multi-centre RCT. Even if this RCT demonstrates no symptomatic relief or improvement in quality of life after trans-venous occlusion, women sufferers and healthcare professionals would benefit from revised diagnostic pathways for the management of CPP with no need to investigate for or treat PVI. Pelvic vein occlusion could be safely abandoned as a treatment for CPP.

**Research questions**

We plan to conduct a pragmatic randomised control trial (RCT) in women aged 18-54 with pelvic vein incompetence and chronic pelvic pain to answer the following research questions:

**Primary**

1. Does treatment of PVI by trans-venous occlusion improve symptoms of CPP assessed using the validated SF-MPQ?

**Secondary**

1. Does treatment of PVI by trans-venous occlusion improve health status measured by the EuroQol (EQ-5D-3 level) in women with CPP?
2. What are the NHS costs of treatment over six months in both treatment groups?
3. What are the key drivers of the relative cost-effectiveness of coil occlusion compared with no treatment for women with PVI? This study will be the first RCT to explore the impact of treating PVI in women with CPP.

Methods

Study design

We propose a balanced (1:1) randomisation, single-blinded parallel group study conducted in the Northwest of England to investigate the clinical and cost-effectiveness of pelvic vein occlusion in the management of pelvic vein incompetence, conducted in accordance with CONSORT guidance. Three centres will identify potential patients (University Hospital of South Manchester, Central Manchester Foundation Trust and Stockport Foundation Trust). Only one centre (University Hospital of South Manchester) will conduct the study visits for diagnosis and treatment.

Inclusion/exclusion Criteria

Inclusion

Women aged 18-54 (inclusive)

Chronic pelvic pain: constant or intermittent lower abdominal or pelvic pain lasting for more than six months diagnosed by a gynaecologist (not specifically associated with sexual intercourse or the menstrual cycle). Diagnosis will be made
clinically based on history and examination which may include diagnostic laparoscopy.

**Exclusion criteria**

Pregnant or within 12 months of pregnancy

Alternative pathologies that may cause chronic pelvic pain (such as endometriosis, adenomyosis, interstitial cystitis or musculoskeletal pain)

Previous hysterectomy

Renal failure (eGRF <30ml/min/1.73m²)

Previous cardiovascular event such as myocardial infarction, stroke, angina or history of heart failure

A diagnosis of malignancy or treated for malignancy over the last 12 months

At increased risk of bleeding such as patients on anticoagulation or history of hereditary bleeding disorders

Chronic disability that impairs mobility

Unable to give informed consent

Unable to comprehend written and spoken English language

**Setting**

Participants will be recruited from the two largest women’s health centres in the north west of England (UHSM and CMFT) as well as a peripheral district general hospital (TH). Participants will be recruited from the general gynaecology clinics within the two hospitals. Standardised investigation of pelvic vein incompetence by trans-vaginal ultrasound (TVU) will be performed by an experienced team
based in the Vascular Studies Unit at UHSM. Trans-catheter occlusion of incompetent pelvic veins will be performed in the interventional vascular radiology suite at CMFT or UHSM.

**Recruitment**

Women with chronic pelvic pain with alternative causes for pelvic pain excluded by a gynaecologist, will be referred to the research team and given an information sheet by their clinician. Once informed written consent has been obtained by the research fellow, participants will undergo a standardised TVU to detect pelvic vein incompetence of the ovarian and internal iliac veins bilaterally.

All participants will be asked to undertake a pregnancy test unless they are on a suitable form of contraception or can re-assure us they are not pregnant. Only participants confirmed to have pelvic vein incompetence on TVU and reflux venography will be randomised into either the treatment or control group.

A potential barrier to recruitment is the thought that if a participant is enrolled to the control group, they would not actually receive treatment despite taking the time and effort to enrolling into the study. One potential method of removing this barrier is to provide all the women who are randomised into the control treatment by coil embolisation at the end of the study if it is shown to be a successful form of treatment.

**Randomisation**

**Sequence generation:** A computer-generated variable block randomisation will be derived by the Medical Statistics Team at the Northwest Royal College of Surgeons Clinical Trials Unit (NWSCTU) based in Liverpool. Participants will be assigned in equal numbers (1:1) after reflux venography to either:
1) coil embolization
2) no intervention

Randomisation will be stratified for either i) ovarian vein incompetence ii) internal iliac vein incompetence and iii) both ovarian and internal iliac vein incompetence.

**Allocation concealment:** Once pelvic vein incompetence has been confirmed on venography, the Radiologist will use an online randomisation line designed by the NWSCTU to determine allocation. The allocation will be reported to the Radiologist who will then either proceed to coil embolization or terminate the procedure.

**Blinding:** The participant will be blinded to their allocation. This will be maintained during the procedure using headphones to play music with or without an additional screen to shield the monitors from view if deemed necessary. The researchers and responsible gynaecologist will also be blinded to the group allocation. The procedures (both the venography and the venography with embolization) can take between 30 minutes to 90 minutes depending on difficulty. Participants will be informed of the variety in completion time and therefore cannot assume that undergoing a prolonged procedure would mean then have undergone intervention. Blinding will also be checked by the research team. At random, twenty participants will be asked to report which group they think they were randomised to; at the end of the study this will be checked against the actual randomisation procedure to determine if the participants were successfully blinded.
Diagnosis and intervention

**Trans-vaginal ultrasound:** We developed a standardised and validated protocol for the detection of pelvic vein incompetence using TVU. The trans-vaginal duplex probe (Phillips iU22 scanner with C10-3v purewave transducer) will be introduced into the vagina with the patient in a supine position. The presence of reflux in the ovarian, internal iliac and para-uterine veins on both sides will be assessed by Valsalva and thigh compression and release. The presence of reflux will then be assessed in the semi-erect position. Sustained reverse flow of > 0.5 seconds will be reported as venous incompetence. The entire investigation takes approximately 15-20 minutes and was not described as painful or uncomfortable by women who took part in our preliminary study.

Several studies have demonstrated consistent accuracy and reliability when comparing TVU with reflux venography which is considered the reference standard. The results of TVU will be reported to all participants and their GP/gynaecologist with an explanation of the significance of the findings. Only participants confirmed to have pelvic vein incompetence on TVU will be randomised into the study.

**Catheter venography:** For this study, catheter venography via the right jugular vein will be performed. The patient will be tilted 5-10° ‘head down’ during the access procedure. This will facilitate jugular cannulation in addition to emptying the pelvic veins. Catheter venography will then be performed by accessing the left and right ovarian veins, and the left and right internal iliac veins. As each target vein is catheterised, the patient will then be tilted ‘head up’ to refill the system and identify reflux within the targeted vein.

In the absence of evidence-based and widely accepted diagnostic criteria, this study is required to state a radiological definition. It was agreed by the research team that for the purposes of this study, ‘pelvic vein incompetence’ should be defined as:
a. Sustained retrograde flow for >0.5 seconds along the full length of the ovarian vein;
   
   or

b. Sustained retrograde flow for >0.5 seconds within the internal iliac vein and venographic evidence of either:
   - retrograde flow within variceal veins draining directly into the internal iliac vein
     
     or
   - varices extending beyond the inguinal ligament into the thigh.

**Catheter venography + Trans-catheter occlusion:** If the diagnosis of pelvic vein incompetence is made, and the patient is randomised to the treatment arm, endovenous occlusion will be performed. In this study, the radiologist may use either distal metallic and proximal coils with sclerotherapy foam (injectable Polidocanol 1%) sandwiched in between, or sclerotherapy foam alone. In the internal iliac veins, coil embolization will only be performed to 2\textsuperscript{nd} order branch veins which are incompetent, and not pursued into 3\textsuperscript{rd} or subsequent order branches into the buttock or thigh. Selective right ovarian vein study will be performed by direct cannulation of the IVC or by injecting X-ray contrast into the IVC at the level of the right renal vein and by stimulating reflux into an incompetent right ovarian vein by Valsalva or thigh compression and release. To confirm effective occlusion, repeat venography will be performed for each treated vein.

Most patients will be discharged 2-3 hours post-procedure. Analgesia is usually not required but patients are advised that they should have Paracetamol or a similar analgesia available at home.
Outcome measures and follow up

1. **Short Form McGill Pain Score (SF-MPQ):** This validated pain score was chosen as our primary outcome score because it imposes minimal burden on respondents and is easily administered. A review of previous RCT’s have shown the visual analogue score (VAS) and the SF-MPQ to be the most frequently used outcome tools in chronic pelvic pain studies in women. The SF-MPQ is a multi-dimensional measure of perceived pain and is also included in the International Pelvic Pain Society Assessment Form. The main component of the SF-MPQ consists of 15 descriptors (11 sensory, 4 affective) which are rated on an intensity scale (0=none, 1=mild, 2=moderate, 3 severe). Total pain score is derived from the sum of the intensity rank values of the words chosen for the total descriptors (max score 45; min score 0). The sum for the individual sensory and affective descriptors will also be calculated.

2. **EQ-5D-3 Level:** The EQ-5D-3L has been extensively validated and has gained widespread use due to its simplicity. It imposes minimal burden on the respondent. The score will be completed at baseline, followed by 1 week, 3, 6 and 12 months following intervention. The scores will be weighted using the weighting scale and compared (minimum score -0.594 to maximum 1.0).

3. **Use of healthcare resources:** All participants will be asked to record their use of healthcare resources specific to the symptoms of PVI and related pain (including VAS scores) over the last one menstrual cycle (or four weeks). At baseline, participants will be asked to record their use of healthcare resources in the last six months prior to recruitment. Then at the pre-specified follow up time points, participants will be asked to indicate their use of healthcare resources over the relevant timeframe using questions that were piloted in a previous case control study. Women will also be asked to indicate if they have missed days at work because of their PVI symptoms. If women have indicated they required subsequent in-patient stay because of their PVI, then the relevant medical notes will be sourced and used to accurately record the types of resources used.
4. Pain symptoms: As well as the above outcome measures, participants will also be asked to respond to questions regarding pain symptoms, impact on their daily activities, menstrual cycle and the presence of varicose veins. Participants will be asked to recall symptoms over a four week period to include a complete menstrual cycle. The questionnaire used in this study is illustrated in Appendix 5.

Alternative or additional outcome measures that could have been used in the study include the anxiety score such as the GAD-7 or the Patient Health Questionnaire (PHQ-9), or more specific gynaecological scores such as the International pelvic pain questionnaire. However adding additional scores to the study would not provide much more additional information but increase the burden expected on participants and risk increasing lost to follow-up. Therefore it was decided to retain the SF-MPQ and the EQ5D as primary outcome measures.

Follow-up

All participants will be asked to complete the outcome measures before randomisation initially, followed by four further recordings at 1 week, 3 months, 6 months and 12 months after intervention. We have chosen these time periods to record the immediate impact of treatment (and document any adverse event/complication), as well as getting the long-term impact on chronic pelvic pain symptoms. The outcome measures will all be conducted via post, online or via phone. Pain scores and health status from the initial assessment to a single time point (3 months) will be carried out will be the primary statistical endpoint.
Statistical and economic analysis

Power calculation

The mean (SD) SF-MPQ score for 483 women with chronic pelvic pain was reported to be 10.4 (7.4). The smallest difference in the SF-MPQ considered in the literature to be clinically important is reported to be five points. Our PPI group and women’s health experts agreed that this absolute difference would be clinically important in the proposed RCT and so this five-point difference was used as the basis of this power calculation. Existing literature was used to formulate the power calculation rather than results of the pilot studies because the previous exploratory study presented in Chapter 4 aimed to highlight symptoms suffered by women with PVI and reviewed the use of a newly-designed outcome measure. The use of the minimally important clinical difference (MICD) based on existing literature is a recognised method of undertaking a power calculation.

Based on these data, we would need 36 subjects in each group to detect this 5-point difference between the groups using an unpaired t-test at the conventional 5% significance level, assuming the published sd of 7.4. This sample size was inflated by 10% to incorporate potential confounding factors in a covariance regression model (although such an adjustment should increase the statistical power). A further 10% was added to compensate for possible loss to follow-up. The total number of subjects in each group will then be rounded up to 50 (100 in total).

The Northwest Royal College of Surgeons Clinical Trials Unit will be responsible for managing the trial database. An intention-to-treat analysis will be used. Comparison of changes in pain scores and health status from the initial assessments to a single time point (1 week or 3 months) will be carried out using multiple linear regression analysis (analysis of covariance) with adjustment for stratification variables and baseline values. Across group analysis will be performed Longitudinal regression analysis (using generalised estimating equations) will be performed to compare changes in these scores in the two
treatment groups over the entire follow-up period to twelve months (incorporating the 1 week, 3, 6 and 12 month assessments).

Economic analysis

The economic analysis will comprise two approaches (i) within-trial and (ii) model-based cost-effectiveness with value of information analysis. The within-trial analysis will quantify the incremental costs (using the trial resource use data), taking the NHS perspective, and incremental benefits (using the trial EQ-5D-3L data), and analyse these data using descriptive statistics, including measures of variation. Healthcare resource use will be translated into costs using published sources of unit cost data such as the NHS reference costs.

After accounting for missing data, regression-based methods will be used to identify the potential key drivers of relative cost-effectiveness of the intervention compared with current practice over the trial time-horizon.

A simple decision-analytic model will then be structured to represent the care pathways for the intervention compared with current practice, which will extend the analysis to understand the relative costs and benefits over a lifetime horizon. This model will assume the NHS perspective for costs and calculate patient benefits in terms of QALYs, using the data collected during the trial, supplemented, where necessary, with data identified from other sources such as systematic reviews of relevant clinical and cost data and input from expert opinion. Using a decision-analytic framework allows for a formal value of information analysis (calculating the expected value of perfect information) on the value of further research work in this area. This will provide values to guide recommendations for how much should be spent on new research to reduce the level of uncertainty in the current evidence base.
Study procedures

Study participants will be expected to complete two visits to UHSM and four follow-ups in total from consent to study termination (table 16).

Table 16 Planned study visits

<table>
<thead>
<tr>
<th>Visit 1 (Screening) conducted at UHSM</th>
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<tbody>
<tr>
<td>The following will be completed at screening:</td>
</tr>
<tr>
<td>• Obtain written informed consent</td>
</tr>
<tr>
<td>• Complete inclusion/exclusion criteria</td>
</tr>
<tr>
<td>• Record demographics, relevant medical history</td>
</tr>
<tr>
<td>• Perform mandatory trans-vaginal duplex ultrasound</td>
</tr>
<tr>
<td>• Perform venepuncture for full blood count, coagulation profile and renal function (in patients confirmed to have incompetence on ultrasound)</td>
</tr>
<tr>
<td>• Complete SF-MPQ and EQ-5D-3L</td>
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</table>

<table>
<thead>
<tr>
<th>Visit 2 (intervention) conducted at UHSM</th>
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</thead>
<tbody>
<tr>
<td>During this visit, the following will be completed:</td>
</tr>
<tr>
<td>• Complete SF-MPQ and EQ5D pre-operatively</td>
</tr>
<tr>
<td>• Reflux venography +/- coil embolization</td>
</tr>
<tr>
<td>• Record any adverse events/complications during the procedure and hospitalisation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow up 1 (one week after intervention)</th>
</tr>
</thead>
<tbody>
<tr>
<td>This visit will be conducted by either post, telephone or online. The following will be completed:</td>
</tr>
<tr>
<td>• Perform and document patient status check to include safety and symptomatic efficacy outcomes. Record any adverse events reported by the patient</td>
</tr>
<tr>
<td>• Complete SF-MPQ and EQ-5D-3L</td>
</tr>
<tr>
<td>• Record use of healthcare resources</td>
</tr>
</tbody>
</table>
**Follow up 2 (three months after intervention)**

This visit will be conducted by either post, telephone or online. The following will be completed:

- Perform and document patient status check to include safety and symptomatic efficacy outcomes. Record any adverse events reported by the patient.
- Complete SF-MPQ and EQ-5D-3L
- Record use of healthcare resources

**Follow up 3 (six months after intervention)**

This visit will be conducted by either post, telephone or online. The following will be completed:

- Perform and document patient status check to include safety and symptomatic efficacy outcomes. Record any adverse events reported by the patient.
- Complete SF-MPQ and EQ-5D-3L
- Record use of healthcare resources

**Follow up 4 (Study Termination-12 months after intervention)**

This visit will be conducted by either post, telephone or online. The following will be completed:

- Perform and document patient status check to include safety and symptomatic efficacy outcomes. Record any adverse events reported by the patient.
- Complete SF-MPQ and EQ-5D-3L
- Record use of healthcare resources

**Early Termination from the Study**

Study termination is defined as the completion of all study requirements and follow-ups listed under study procedures thorough to follow-up 4. Early termination may occur if:
In the opinion of the investigator, the patient cannot safely perform the study procedures required by the protocol. This patient will still be followed for safety and symptomatic efficacy through to follow-up 4.

The patient decides to withdraw consent from any further trial participation. This will be identified at the subsequent follow-up when the patient is contacted by the research team, or earlier if the patient contacts the research team.

Patient death. The patient’s GP will be informed of the participant’s involvement in the trial and will be asked to inform the research team if this occurs.

Patient is lost to follow-up and the efforts to obtain follow-up are appropriately documented in the patient’s source documentation.

Patients are free to withdraw from the study at any time for any reason. However all efforts will be made to follow patients for the full duration of the study and to encourage all patients to complete the outcome measures.

**Ethics**

All aspects of the project will comply with Good Clinical Practice and the Declaration of Helsinki. All participants will be asked for written informed consent. We will not be withholding any form of standard medical practice. The patient’s usual medical care will be provided by their gynaecologist and/or GP. Local ethics committee approval was obtained (reference 15.NW.0360).

**Confidentiality**

The research team will ensure that the patient’s confidentiality is maintained. Patients will be identified on documents submitted to the sponsor by their patient identification number. Documents that are not for submission to the sponsor will be kept in a secure room accessed by the chief or sub investigator only.
**Ethical considerations and risks**

Trans-vaginal duplex ultrasound is a harmless internal examination using ultrasound which is safe with no side effects. It is a well-recognised form of investigation in women with chronic pelvic pain and widely accepted by women suffering from pelvic symptoms. The trans-vaginal ultrasound scan is not usually painful or uncomfortable, and has been well tolerated in over 100 women who have undergone the examination for previous studies.

Trans-venous occlusion involves very few side effects. There is a small risk of damage to adjacent tissues during jugular puncture which includes arterial injury and pneumothorax. This occurred in less than 9 in 100 patients who have undergone the procedure in published medical reports. This risk is minimised by performing the jugular puncture under ultrasound guidance. There is also a small risk of haematoma and infection around the puncture site. The haematoma will subside over the course of 1-2 weeks whilst infections around the site may require antibiotics.

There is a slight risk of an allergic reaction to the dye or infection after treatment, although this has not been reported in any of the published reports we have reviewed. Coil migration into the pulmonary circulation has been reported to occur in approximately 2 in 100 patients. No long term complications or deaths were reported in any of these studies.

All patients will be required to take a pregnancy test or provide suitable evidence that they are not pregnant. The diagnostic radiation exposure involved in this study will depend on which arm of the study the subject is randomised to. Subjects randomised to the venography’ arm will receive a single event of reflux venography (local dose estimate 2.5 mSv effective dose from national audit figures on similar examinations). Subjects randomised to the ‘trans venous coil occlusion’ arm will receive a single trans-venous occlusion procedure, including prior reflux venography and post occlusion venography (local dose estimate 15 mSv effective dose from a small local DAP survey: typical DAP 120 Gy cm2). For a participant in normal health, there would be an extra risk of cancer induction due to exposure to
radiation. For an adult female, the estimated lifetime risk of cancer associated with the reflux venography dose is approximately 1 in 8200, placing this arm of the study into the ‘Intermediate’ risk category. The corresponding estimated lifetime risk of cancer associated with the trans-venous occlusion dose is approximately 1 in 1400, placing this arm into the ‘Moderate’ risk category. The latency period for expression of a radiation induced solid cancer is of the order of 10 years.

Data retention

Clinical Research Forms will be securely stored for 15 years after completion of the study. Electronic copies of the study data set will be retained indefinitely, and after a period of three years will be made available to other investigators on request and subject to a data sharing agreement.

Monitoring and safety reporting

The study will have a Trial Steering Committee (comprising three independent members and 2 team members. The three independent committee members will review safety, recruitment and ethical data, and would be able to close the study if concerns are raised. We will use a risk-adapted approach to monitoring. Recruitment and progress against milestones will be monitored by the study team at monthly Trial Management Meetings. A quality assurance programme will ensure consistent and high quality approaches to consent and implementation of the clinical rule. We will define an adverse event as one that occurs directly as a result of the intervention and would not have been anticipated as part of clinical management at initial presentation.
Research governance

The research will be sponsored by the University Hospital of South Manchester (with appropriate insurance policies in place). This study will be fully compliant with the research governance framework and MRC Good Clinical Practice guidelines.

Trial management

Trial timeline

We propose a 30-month study period beginning in June 2015. We will begin governance and approval processes in the pre-funding stage and have approvals in place to commence recruitment in June 2015. We expect patient identification and recruitment to take approximately 12 months, with follow-up of participants to continue until month 12. Data cleaning, analysis and final reporting will be carried out over the last six months of the project.

Management

The Manchester Pelvic Vein Team will meet monthly chaired by the Chief Investigator to report on recruitment, adverse events and trial progress.

Steering Committee: The trial will be regulated and monitored by an independent Steering Committee with an independent Chairman approved by NIHR, who will appoint the biomedical statistician (with RCT experience) of their choice and, if they wish, a pain specialist. The Steering Committee will address trial design, methodology, recruitment and any issues that they consider might introduce a bias. The Steering Committee will meet quarterly during the trial period to ensure that recruitment and trial progress is on target.
**Data Monitoring and Stopping Committee:** As this is the first RCT to study outcomes following coil occlusion for pelvic vein incompetence, and as the outcome measures are not life or limb threatening, there is no place for an interim analysis in a study recruiting 100 patients. We do not believe that there will be a need for a Data Monitoring or Stopping Committee.

**Patient and Public Involvement Group:** Our PPI group includes ten women with CPP of which six have PVI. One member has experienced treatment by coil embolization privately. The PPI group has guided the throughout our studies and the design of this RCT by helping to design the study treatment pathways, as well choosing patient related functional outcome scores to be used to characterize patients with and without PVI. They pilot tested our questionnaires, ensuring they were clearly written with no medical jargon.
Figure 20 PRISMA flow diagram of the RCT

Female, CPP
Referred to research team/ given PIS and reply slip

Inc/Exc criteria
Ultrasound at UHSM
Consent form signed
collection of demographic data
Completion of outcome measures

PVI identified on ultrasound
PVI not identified on ultrasound

Rex reflux venography
Completion of outcome measures

Refused back to responsible clinician
with ultrasound report

PVI not identified
PVI confirmed

Refused back to responsible clinician
with TVU + venography report

Randomisation by LCTU during
procedure

Emboliisation
No emboliisation

Follow up:
1 week, 3 months, 6 months, 12 months

Follow up:
1 week, 3 months, 6 months, 12 months
Chapter summary

This RCT is vital in providing definitive answers to whether PVI is a cause for CPP in women and is a logical follow-on study from the work presented in this thesis. We have established in a case-control study that there is an association between PVI and CPP, but this evidence is not enough to categorically state whether PVI is responsible for CPP and whether treatment using coil occlusion is effective. The RCT will also provide data on the accuracy of TVU and will allow for a larger number of comparisons to be made with reflux venography.

The systematic review in Chapter 8 highlighted the weakness and inadequacies of previous studies attempting to answer similar research questions. This trial was therefore designed by following good practice guidance such as the CONSORT guidance to ensure it was as robust as possible.
CHAPTER 10: DISCUSSION

Summary of main findings

The studies included in this thesis have described the common symptomatology experienced by women with PVI, highlighted the accuracy of diagnosis by trans-vaginal ultrasound and demonstrated a significant association between PVI and CPP in a well-designed case-control study. The weakness of the evidence for the use of invasive treatments (primarily trans-venous occlusion) was exposed using a systematic review. In light of these data, a randomised control trial was designed; funding for this has now been secured from the NIHR Research for Patient Benefit (RfPB) programme, although it is yet to commence.

The findings showed that women with PVI experience a greater frequency of pelvic pain and reduced health-related quality of life compared with healthy women. They are also greater users of NHS resources, with a greater number of hospital admissions and outpatient attendances than both women with leg varicose veins and healthy controls without pelvic or leg vein incompetence. This characterisation study had significant strengths over comparable research which was predominantly case reports and case series because it included a larger sample of women and made direct comparisons to two control groups. Another unique feature of this study to was the assessment tool used. A questionnaire was created using questions extracted from several well-known gynaecological and pain patient reported outcome measures (PROM) producing an assessment tool which provided data on quality of life (using the EQ-5D in its entirety), pain symptoms, menstrual cycle and varicose vein history. One acknowledged the fact that customising an existing validated tool would in-validate its use to produce a comparable score; since the aim of the study was not to determine pain or menstrual scores but to provide as much information as possible on symptomatology.
TVU is increasingly used as an imaging modality for the diagnosis of PVI. The retrospective review of 50 women who underwent a TVU undertaken for this thesis shows that when performed in the supine and semi-standing position with Valsalva, pelvic vein reflux is at its most visible. Quite often pelvic veins would appear incompetent in supine, but when assessed in the semi-standing position would demonstrate no reflux. This suggests that reflux in the supine position alone is not enough evidence to diagnose PVI, since there is not enough gravitational pressure to close the valves within the vein. These data imply that patients who demonstrate reflux in supine, but no reflux in semi-standing should not be classified as having PVI, as the valves are competent when put under pressure. Although the presence of reflux in semi-standing is more significant, the scan is still performed in supine initially, because visibility is poorer during the semi-standing position. This has significant implications for future research and the performance of these scans in a clinic setting. There is currently no standardised protocol on how TVU should be performed or its criteria for diagnosing PVI. The criteria we have used (reflux time of >0.5s in one or more veins) was determined by expert opinion and in consultation with several clinicians and sonographers. The reflux time of 0.5s is also used to diagnose reflux in superficial veins of the leg and has been a long established diagnostic criteria for the last two decades. However there is an argument to whether this reflux time cut-off should be increased up to one second which is the universal reference range used for the diagnosis of deep vein incompetence. Going forward, consideration needs to be given to the diagnostic criteria for PVI (including duration of reflux) to ensure that it is not over diagnosed and only those with significant reflux are entered into further research trials or considered for experimental treatments.

When compared against reflux venography which is considered the reference standard, individual agreement was good. This study is the first to directly comparing TVU with reflux venography in the diagnosis of PVI. In spite of the new evidence highlighted in this study, its small sample size and inability to determine sensitivity and specificity mean is not enough to recommend a change in practice and it could not determine TVU accuracy. Participants in this study were only
referred for reflux venography if they had a positive TVU scan, exposing this study at risk of partial-verification bias. This study showed that although TVU was able to correctly determine whether a patient had PVI or not, the actual individual agreement with regards to which veins were incompetent was not good. Without establishing the frequency of correct true negatives it cannot be used to dismiss patients as not having PVI. Therefore in those women who have clear signs or symptoms of PVI and an inconclusive ultrasound scan, reflux venography will still remain the diagnostic test of choice.

Another significant issue identified during this research programme is the lack of diagnostic criteria and technical standardisation for reflux venography; considered the reference standard across the developed world. No interventional radiology guidance was identified to aid the performance of the technique and interpretation of performing reflux venography. In order to formulate a consensus on how reflux venography should be performed and PVI diagnosed, a Delphi study initially amongst members of the British Society of Interventional Radiologist (BSIR) is proposed and support from the BSIR has been received. It is then planned to expand this study into Europe to formulate an international consensus.

The case-control study described in Chapter 7 demonstrated a significant relationship between CPP and PVI. This study attempted to establish whether PVI is associated with CPP and also its prevalence in healthy women. This study although still ongoing, has produced significant results that are of great interest to women with pelvic pain and clinicians. Fundamentally although an association between PVI and CPP does not represent causation, it does provide strength to the argument and supports a RCT to evaluate the effectiveness of treatment. Should the findings to date be upheld by completion of the study, they will support deliberate investigation of PVI in women with CPP in whom all other common causes have been excluded. One of the challenges in this study was the difficulty in identifying a validated PROM which would be appropriate for women with pelvic pain (not endometriosis related). In a similar fashion to the characterisation study, a questionnaire was designed using aspects of pre-existing outcome measures to collect information regarding pain symptoms and their impact on health and
wellbeing. It has become very clear through this research process that a pelvic pain specific PROM is needed urgently.

There is substantial literature evaluating trans-venous occlusion as a treatment for CPP. Almost all of the literature available is observational research with only one quasi-randomised trial identified. All 13 studies discussed in the systematic review reported subjective improvements in pelvic pain after trans-venous occlusion in women with CPP and PCS, but the level of evidence prevents any conclusions about its effectiveness being drawn. The RCT designed as part of this thesis will be the first study to determine the effects of trans-venous occlusion in and unbiased manner.

Key findings from this thesis

- Women with PVI report more and different CPP symptoms when compared with healthy women or women with varicose veins of the leg.

- Women with PVI report poorer health status, measured using the EQ-5D, when compared with healthy women with no PVI.

- TVU could potentially be used as a screening tool for PVI with good inter-observer variability (kappa 0.84), but the accuracy of TVU is still to be determined.

- PVI is strongly associated with CPP with 46% of women with CPP demonstrating PVI on TVU compared with 20% of healthy women with no CPP (p=0.02). However no significant difference was seen in health status and pain symptoms between women with CPP and PVI, and with CPP and no PVI.

- A review of the current evidence has failed to support (or deny) the presence of a causal relationship between PVI and CPP. An RCT of trans-venous occlusion of PVI is required to both address this and assess the efficacy of an increasingly commonly used intervention.
**Strengths and limitations of studies**

This thesis is primarily devised of prospective observational studies. The primary strength of the case-control studies described in Chapter 3 and 7 is successful matching of two control groups matched for age (+/- 2 years) and parity. Comprehensive data were collected about demographics, pain symptoms, and use of healthcare resources. This is the first study to determine the impact of PVI on health status using the EQ-5D-3L score that can be used to determine how interventions can impact their illness and day-to-day activities.

The rigorous TVU scanning protocol performed in women with suspected PVI allowed us to determine which technique was the most effective at demonstrating pelvic vein reflux. This will aid the development of a standardised protocol that will prevent under or over-diagnosis of PVI and allow for comparison of results.

The systematic review of evidence evaluating trans-venous occlusion of pelvic veins for the treatment of CPP was conducted in accordance with existing guidelines for the reporting of systematic reviews of intervention studies. No other review has attempted to evaluate trans-venous occlusion to inform clinical practice. The inability to contact authors regarding missing information was a limitation of this study.

The primary strength of the proposed RCT is the ability to blind participants to treatment or control groups to really determine the impact of treatment. It has been designed as per the CONSORT guidance.

A limitation to the studies are the questionnaires used being subject to recall bias and due to the variable nature of pain symptoms, scores not being a true reflection of the symptoms experienced. A diary was designed to overcome this bias and participants were asked to document daily pain symptoms over the course of a menstrual cycle. This was piloted amongst our PPI group and the response rate and level of completion was very poor and therefore was not included in the formal studies. The questionnaire itself requires validation by content, criterion and construction. Face validity can be assessed by asking respondents to determine
whether the questionnaire measure what is intended, followed by using an expert panel to determine the content validity of the questionnaire. An alternative method would be to assess internal consistency by asking respondents to complete the questionnaire over a number of intervals to determine whether the response is consistent.

The case-control study described in chapter 7 has a relatively small sample size. This was primarily due to difficulties in recruitment. We found it to be relatively easy to identify women with CPP with no formal diagnosis who were keen to be involved in research that may identify a cause for their symptoms. However the level of attendance to appointments to discuss the research or for a TVU scan was very poor. This has been seen in several studies on CPP syndromes and is likely to be due to a combination of personal, social and psychological factors such as obtaining childcare or anxiety of receiving a diagnosis. Anxiety about attending appointments has been frequently reported in pain research.\textsuperscript{169 170}

The RCT is a small-scale study which may impact on generalisability but will provide vital information on the logistical approach a more definitive RCT may want to follow. The studies in this thesis follow the MRC Complex Interventions Framework and this RCT is a necessary precursor to a future definitive trial. We failed to identify a single existing questionnaire or disease specific outcome measure which adequately captured issues relevant to CPP. The patient and public involvement group found the International Pelvic Pain Society questionnaire and the Endometriosis Health Profile (EHP-30) too long. The lack of patient reported outcome measures meant that the McGill Pain questionnaire was agreed for use in the RCT. This is a non-specific pain score and again may not adequately capture issues related to CPP. Work on the development of a CPP specific score is urgently required.
Future research

There are several areas within the topic of PVI and CPP that need continued investigation.

• It is still unclear how PVI can be defined on reflux venography which is supposedly the reference standard investigation. A Delphi study to gain a unanimous consensus amongst UK Interventional Radiologists is currently underway.

• The proposed RCT will determine whether participants can be successfully blinded to the interventional procedures. This will aid the design of future definitive trials on PVI treatment.

• A useful addition to the RCT would be to assess for treatment efficacy by repeating trans-vaginal ultrasound at approximately six-months after the initial procedure to check for signs of recanalization or the development of collateral circulations which may determine a greater probability of symptoms reoccurring.

• The comparative study comparing TVU with reflux-venography needs to be adequately powered (and ideally including women who have had a normal TVU) to determine overall diagnosis sensitivity and specificity.
Final conclusion

The aim of the work presented in this thesis was to advance understanding of PVI and its relationship with CPP in women and this has been achieved. This thesis has added several novel contributions to the field. This includes characterising symptoms associated with PVI, determining the prevalence of PVI in women with CPP and evaluating methods of diagnosis using ultrasound. The studies have culminated in a protocol for a well-designed randomised trial which will, for the first time, enable robust assessment of PVI treatment. The work reported here has the potential to impact on the management of women with CPP in the near future.
CHAPTER 11: REFERENCES


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112. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous,


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CHAPTER 12: APPENDIX
Appendix 1

Questionnaire used in case control studies described in Chapter 4 and 7
**About You**

1. **How old are you** ______ years

2. **Weight** ______ kilograms or, ______ St ______ lbs

3. **Height** ______ feet ______ inches or, ______ cm

4. **Smoking History** *(Please tick one option)*

   Ex-Smoker [ ] When did you stop smoking? ______ years ago

   How many did you smoke a day? ____ a day

   Current Smoker [ ] How many years have you smoked for? ______ years

   How many do you smoke a day? ____ a day

   Never Smoked [ ]

5. **How many times have you been pregnant?**

   Pregnancies ________

   Don't want to answer the question [ ]

6. **How many children have you given birth to?**

   Number of children ________

   Don't want to answer the question [ ]
Your Health Today

We would like to know what your general health is like today.

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

7. Mobility
I have no problems walking about
I have some problems in walking about
I am confined to bed

8. Self-care
I have no problems with self-care
I have some problems washing or dressing myself
I am unable to wash or dress myself

9. Usual activities (e.g. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

10. Pain/Discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

11. Anxiety/Depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed
12. To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
The Menstrual Cycle

These next questions ask you about any menstrual (period) symptoms you may be having.

13. Age you started your periods _____ years old

14. Date your last period started _____/_____/_____

15. Are your periods regular e.g. every month? Yes [ ] No [ ]

16. How long does your typical period last? days

17. Do you bleed in between periods? Yes [ ] No [ ]

18. How would you describe your periods on average? Please tick one option

- Light [ ] If you ticked this box, please move to question 22.
- Moderate [ ] If you ticked this box, please move to question 22.
- Heavy
- Very Heavy [ ]
19. How long have you had heavy periods for? Please tick one option

- 2 months or less
- Between 2 months and 1 year
- More than 1 year
- Don’t know

20. What treatments have you tried for your heavy periods? Please tick all the options that apply.

- None
- The Pill (oral contraception)
- Other medication (not the Pill) Intrauterine system (e.g. Mirena coil)
- Dilation and Curettage (removal of the uterus lining)
- Other treatment
- Don’t know
### 21. During the previous 3 months, how distressed were you by...

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>A great deal</th>
<th>A very great deal</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Heavy bleeding during your menstrual period?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Passing blood clots during your menstrual period?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Fluctuation in the duration of your menstrual period?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Feeling tightness or pressure in your pelvic area?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Feeling need to pass urine during the daytime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Getting up at night to pass urine?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Feeling fatigued?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pain Symptoms

22. Do you experience any pelvic or abdominal pain?
   Yes [ ]
   No [ ] If No, please move to Q34

Over the course of a normal menstrual cycle, which of the following symptoms have you experienced? Please tick Yes or No, and place a cross (X) on the line below demonstrating how severe your pain is.

23. Pain before periods
   Yes [ ] No [ ]

24. Pain during periods
   Yes [ ] No [ ]
25. Pain throughout the month

Yes ☐ No ☐

26. How would you describe the pain? (Please tick all that apply)

- Stabbing ☐
- Spasm ☐
- Burning ☐
- Dull ☐
- Aching ☐
- Sharp ☐
- Throbbing ☐
- Shooting ☐
- Cramping ☐

27. Where do you get the pain? Please mark on the diagram all the places you experience pain.
28. Pain during sexual intercourse

- Yes □
- No □
- Not Applicable □

29. Pain opening bowels during periods

- Yes □
- No □

30. Pain opening bowels at other times

- Yes □
- No □

31. Lower back pain

- Yes □
- No □
32. Feeling Bloated

Yes [ ] No [ ]

![Smiley and sad face icons with percentage scale from 0% to 100%]

33. How often over the last year, because of your pelvic pain have you: *(Please tick one box on each line)*

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Been unable to go to social events because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Been unable to do jobs around the home because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Found it difficult to stand because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Found it difficult to exercise or do the leisure activities you would like to do because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Lost you appetite and/or been unable to eat because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Been unable to sleep properly because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Had to go to bed/lie down because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Been unable to do the things you want to do because of the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Felt unable to cope with the pain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Varicose Veins**

These questions ask about your experience of varicose veins. The answer to these questions will help us understand the relationship between pelvic vein incompetence and leg symptoms.

<table>
<thead>
<tr>
<th>34. During the past 4 weeks, how often have you had any of the following leg problems?</th>
<th>Every day</th>
<th>Several times a week</th>
<th>About once a week</th>
<th>Less than once a week</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Heavy legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Aching legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Night cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Heat or burning sensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Restless legs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Throbbing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h. Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Tingling sensation (pins and needles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

35. Do you suffer from varicose veins? *(These are enlarged veins in your legs)*

Yes  
No  
*If no, please go to question 43.*
36. At what time of day is the discomfort/ache from your varicose veins most intense? (Please tick one option)

On waking ☐ During the night ☐
At mid-day ☐ At any time of day ☐
At the end of the day ☐ No discomfort/ache ☐

37. Compared to one year ago, how would you rate your varicose vein problem in general now? (Please tick one option)

Much better now ☐ Somewhat worse now ☐
Somewhat better now ☐ Much worse now ☐
About the same ☐ I did not have any varicose veins last year ☐

38. During the past 4 weeks, to what extent have your varicose veins interfered with your normal social activities with friends, family or groups? (Please tick one option)

Not at all ☐ Quite a bit ☐
Slightly ☐ Extremely ☐
Moderately ☐

39. How bad has the discomfort/ache in your legs been in the past 4 weeks?
(Please tick one option)

No discomfort/ache ☐ Moderate ☐
Very mild ☐ Severe ☐
Mild ☐ Very severe ☐
40. Have you had surgery for varicose veins in the past?

Yes          
No            If no, please go to question 43.

41. Did your varicose veins reoccur after treatment?

Yes          
No            If no, please go to question 43.

42. How long after surgery, did your varicose veins reoccur?

Within 6 months       
6 – 12 months        
1 - 2 years          
More than 2 years
Use of Healthcare Resources

We are interested in your use of healthcare services over the last year.

43. Over the last year, who have you seen regarding your health? Please tick all that apply

- [ ] GP  - [ ] Specialist Nurse
- [ ] Practice (GP) Nurse  - [ ] Pharmacist/Chemist
- [ ] Consultant/Hospital Doctor  - [ ] Other, please state: ____________________________

44. Over the last year, how many times have you been to see your GP? Please tick one box only

- [ ] Never  - [ ] 5 or 6 times
- [ ] 1 or 2 times  - [ ] More than 6 times
- [ ] 3 or 4 times  - [ ] Do not know

45. Over the last year, how many times have you been to see a hospital doctor?

Please tick one box only

- [ ] Never  - [ ] 5 or 6 times
- [ ] 1 or 2 times  - [ ] More than 6 times
- [ ] 3 or 4 times  - [ ] Do not know

46. If you have seen a hospital doctor, what did they say and treatment did you receive?

………………………………………………………………………………………………………………
………………………………………………………………………………………………………………
47. Have you had been admitted to hospital to have treatment for heavy menstrual bleeding or pelvic pain?

Yes [ ]
No [ ]

If yes, please write the name of the hospital here:

______________________________________________________________________________________________

Please write the date you were admitted (an approximate date is fine)

______________________________________________________________________________________________

48. Have you had an operation for heavy menstrual bleeding or pelvic pain?

Yes [ ]
No [ ]

If yes, please write the name of the operation, or what you can remember about the operation here:

______________________________________________________________________________________________

49. Have you regularly purchased medicines, such as pain killers, or anything else from the pharmacy to help with your heavy menstrual bleeding or pains?

Yes [ ]
No [ ]

If yes, then please write down what you purchased here:

______________________________________________________________________________________________
Appendix 2

Trans-vaginal ultrasound protocol
Scanner Settings:
Phillips iU22 (USA)
Probe C10-3v pure wave
Trans vaginal gynaecological set up

Manual adjustments:
Flow optimisation to image low flow adjusted manually
Doppler sample volume adjusted manually
The transducer or scanner should be adjusted to operate at the highest clinically appropriate frequency, realizing that there is a trade-off between resolution and beam penetration

Patient position:
Supine
Semi-standing (sat on edge of examination couch)
Bladder to be empty
Assessment during quiet respiration and Valsalva during each position

Provocation manoeuvres:
Valsalva: standardised as forceful attempt at exhalation against a closed glottis. Participants are asked to blow into a 20ml syringe for 3-5 seconds.

Comments made on:
Bilateral ovarian veins
Bilateral iliac veins
Para-uterine veins
Appendix 3

Search Strategy
**Medline: 1946 to June 2014**

1. pelvic vein incompetence. ti,ab;

2. (pelvi* OR iliac OR ovary OR ovarian) AND (venous OR vein*) AND incompeten* ti,ab;

3. Pvi ti,ab;

4. pelvi*AND (varicosit* OR varicocele* OR congest*). ti,ab;

5. congestion syndrome. ti,ab;

6. pelvi* AND varicose AND vein* ti,ab;

7. pelvi* AND (vein OR venous) AND dilatation* ti,ab;

8. pelvi* adj1 pain* ti,ab;

9. pelvi* OR abdom*) adj1 pain* ti,ab:

10. noncyclical AND chronic AND pelv* AND pain* ti,ab;

11. iatrogenic AND pelv* AND pain* ti,ab;

12. exp Pelvic Pain/ or chronic pelvic pain.mp:

13. Pelvis/[bs]

14. Iliac vein/[ab,pp,ra,us]

15. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14

16. Treatment.ti,ab;

17. emboli* ti,ab;

18. therapeudic. ti,ab:

19. sclerotherap* OR Occlusion ti,ab;

20. sclerotherapy/

21. endovascular surgery ti,ab;

22. 16 OR 17 OR 18 OR 19 OR 20 OR 21

23. 15 AND 22
EMBASE: 1974 to June 2014

1. pelvic vein incompetence. ti,ab;

2. (pelvi* OR iliac OR ovary OR ovarian) AND (venous OR vein*) AND incompeten* ti,ab;

3. Pvi ti,ab;

4. pelvi*AND (varicosit* OR varicocele* OR congest*). ti,ab;

5. congestion syndrome. ti,ab;

6. pelvi* AND varicose AND vein* ti,ab;

7. pelvi* AND (vein OR venous) AND dilatation* ti,ab;

8. pelvi* adj1 pain* ti,ab;

9. pelvi* OR abdom*) adj1 pain* ti,ab:

10. noncyclical AND chronic AND pelv* AND pain* ti,ab;

11. iatrogenic AND pelv* AND pain* ti,ab;

12. exp Pelvic Pain/ or chronic pelvic pain.mp:

13. Pelvis/[bs]

14. Iliac vein/[ab,pp,ra,su,us]

15. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14

16. Treatment.ti,ab;

17. emboli* ti,ab;

18. therapeutic. ti,ab:

19. sclerotherap* OR Occlusion ti,ab;

20. sclerotherapy/

21. endovascular surgery ti,ab;

22. 16 OR 17 OR 18 OR 19 OR 20 OR 21

23. 15 AND 22
CINAHL: 1981 TO 2014

1. pelvic AND vein AND incompetence. ti,ab;

2. (pelvi* OR iliac OR ovary OR ovarian) AND (venous OR vein*) AND incompeten* ti,ab;

3. Pvi ti,ab;

4. pelvi*AND (varicosit* OR varicocele OR congest*). ti,ab;

5. (congestion AND syndrome). ti,ab;

6. pelvi* AND varicose AND vein* ti,ab;

7. pelvi* AND (vein OR venous) AND dilatation* ti,ab;

8. exp PELVIC PAIN/ OR exp CHRONIC PAIN/

9. exp ABDOMINAL PAIN/ OR exp PELVIC PAIN/

10. chronic AND pelv* AND pain ti,ab;

11. ILIAC VEIN/ OR MAY-THURNER SYNDROME/

12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11

13. treatment. ti,ab;

14. emboli* ti,ab;

15. therapeutic. ti,ab:

16. sclerotherap* OR Occlusion ti,ab;

17. SCLEROTHERAPY/

18. (endovascular AND surgery) ti,ab;

19. 13 OR 14 OR 15 OR 16 OR 17 OR 18

20. 12 AND 19
British Nursing index: 1992 to 2014

1. Pvi ti,ab;
2. pelvi*AND (varicosit* OR varicocele OR congest*). ti,ab;
3. (congestion AND syndrome). ti,ab;
4. pelvi* AND varicose AND vein* ti,ab;
5. exp PELVIC PAIN/OR exp CHRONIC PAIN/
6. chronic AND pelv* AND pain ti,ab;
7. (abdominal AND pain) ti,ab;
8. pelvis.ti,ab;
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. treatment.ti,ab;
11. emboli* ti,ab;
12. therapeutic. ti,ab:
13. sclerotherap* OR Occlusion ti,ab;
14. (endovascular AND surgery) ti,ab;
15. 10 OR 11 OR 12 OR 13 OR 14
16. 9 AND 15

Cochrane Library; searched in June 2014

Title, abstract, keyword

1. Pelvic vein incompetence
2. PVI
3. Pelvic congestion syndrome
4. Vein occlusion
5. Embolisation
6. Vein sclerotherapy
Web of Science; searched in June 2014

1. Pelvic vein incompetence
2. Pelvic congestion syndrome
3. Congestion syndrome
4. Chronic pelvic pain
5. Ovarian vein
6. CPP
7. PVI
8. PCS
9. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10. Embolisation
11. Coil embolization
12. Occlusion
13. Endovascular
14. Vascular
15. 10 OR 11 OR 12 OR 13 OR 14
16 9 AND 15
Appendix 4

Checklist for inclusion into study
Trans-venous occlusion of incompetent pelvic veins as a treatment for chronic pelvic pain in women: a randomised controlled trial

Participant Name: _____________________________________________________

Date of Birth: _________________________________________________________

Study ID: ______________________________________________________________

Inclusion (both criteria must be met)

Aged 18-54 (inclusive)

Chronic pelvic pain diagnosis

Exclusion criteria (one or more ticks excludes patient from this trial)

Pregnant or within 12 months of pregnancy

Diagnosis of endometriosis, adenomyosis, interstitial cystitis or musculoskeletal pain

Previous hysterectomy

Renal failure (eGFR <30ml/min/1.73m²)

Diagnosis of myocardial infarction, stroke, angina or history of heart failure

Diagnosis of malignancy or treated for malignancy over the last 12 months

At increased risk of bleeding or on anticoagulation or history of hereditary bleeding disorders

Chronic disability that impairs mobility

Unable to give informed consent

Unable to comprehend written and spoken English language
Appendix 5

Questionnaire used in randomised control trial
1. **Your Health Today**

We would like to know what your general health is like **today**.

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

**Mobility**
- I have no problems walking about
- I have some problems in walking about
- I am confined to bed

**Self-care**
- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual activities** (e.g. work, study, housework, family or leisure activities)
- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.
2. Your pain today

The words below describe average pain. Place a check mark (✓) in the column that represents the degree in which you feel that type of pain. Please limit yourself to a description of the pain in your pelvic area only.

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>NONE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Shooting</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Stabbing</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Sharp</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Cramping</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Gnawing</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Hot-Burning</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Aching</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Heavy</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Tender</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Splitting</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Tiring-Exhausting</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Sickening</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Fearful</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
<tr>
<td>Punishing-Cruel</td>
<td>0)</td>
<td>1)</td>
<td>2)</td>
<td>3)</td>
</tr>
</tbody>
</table>

**Present Pain Intensity (PPI)**

Tick along the scale below for pelvic pain

| No Pain | | Worst possible pain |
|---------|----------------|

193
Please place a check mark (✓) in the appropriate column for your present pain.

0  No pain  ______
1  Mild      ______
2  Discomforting ______
3  Distressing ______
4  Horrible   ______
5  Excruciating ______
3. Pain Symptoms

Over the course of a normal menstrual cycle, which of the following symptoms have you experienced? Please tick Yes or No, and place a cross (X) on the line below demonstrating how severe your pain is.

Pain before periods

Yes ☐ No ☐

Pain during periods

Yes ☐ No ☐

Pain throughout the month

Yes ☐ No ☐
Where do you get the pain? Please mark on the diagram all the places you experience pain.

Pain during sexual intercourse

Yes ☐  No ☐  Not Applicable ☐
4. Varicose Veins

Do you suffer from varicose veins? *These are enlarged veins in your legs*

Yes [ ]

No [ ] *If no, please go to question 34*

Please draw in your varicose veins on these diagrams

![Legs viewed from front](image1)
![Legs viewed from back](image2)

In the last 2 weeks for how many days did your veins cause you pain or ache?

- None at all [ ]
- Between 1 and 5 days [ ]
- Between 6 and 10 days [ ]
- For more than 10 days [ ]
During the last two weeks, on how many days did you take painkilling tablets for your varicose veins?

None at all
Between 1 and 5 days
Between 6 and 10 days
For more than 10 days

In the last two weeks, how much ankle swelling have you had?

None at all
Between 1 and 5 days
Between 6 and 10 days
For more than 10 days

In the last two weeks, have you worn support stockings or tights?

No
Yes, those I bought myself without prescription
Yes, those prescribed by my doctor which I wear occasionally
Yes, those prescribed by my doctor

In the past two weeks, have you had any itching in association with your varicose veins?

No
Yes, above the knee only
Yes, below the knee only
Yes, above and below the knee

Do you have purple discolouration caused by tiny blood vessels in the skin in association with your varicose veins?
Do you have a rash or eczema in the area of your ankle?

<table>
<thead>
<tr>
<th></th>
<th>Right Leg</th>
<th>Left Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, but it does not require treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, and it requires treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you have a skin ulcer associated with your varicose veins?

<table>
<thead>
<tr>
<th></th>
<th>Right Leg</th>
<th>Left Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does the appearance of your varicose veins cause you concern?

<table>
<thead>
<tr>
<th></th>
<th>Right Leg</th>
<th>Left Leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, their appearance causes me slight concern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, their appearance causes me moderate concern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, their appearance causes me a great deal of concern</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Does the appearance of your varicose veins influence your choice of clothing including tights?

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
</tr>
<tr>
<td>Occasionally</td>
</tr>
<tr>
<td>Often</td>
</tr>
<tr>
<td>Always</td>
</tr>
</tbody>
</table>
During the last two weeks, have your varicose veins interfered with your work/housework or other activities?

No  
I have been able to work but my work has suffered to a slight extent  
I have been able to work but my work has suffered to a moderate extent  
My veins have prevented me working one day or more

During the last two weeks, have your varicose veins interfered with you leisure activities? (including sport, hobbies and social life)

No  
Yes, my enjoyment has suffered to a slight extent  
Yes, my enjoyment has suffered to a moderate extent  
Yes, my veins have prevented me taking part in any leisure activities
5. Use of Healthcare Resources

We are interested in your use of healthcare services over the last four weeks.

**Over the last four weeks, who have you seen regarding your pelvic pain or menstrual symptoms? Please tick all that apply**

<table>
<thead>
<tr>
<th>Health Professional</th>
<th>Ticking Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td></td>
</tr>
<tr>
<td>Specialist Nurse</td>
<td></td>
</tr>
<tr>
<td>Practice (GP) Nurse</td>
<td></td>
</tr>
<tr>
<td>Pharmacist/Chemist</td>
<td></td>
</tr>
<tr>
<td>Consultant/Hospital Doctor</td>
<td>Other, please state: _____________</td>
</tr>
</tbody>
</table>

**Over the last (timeframe TBC), how many times have you been to see your GP? Please tick one box only**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Ticking Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>5 or 6 times</td>
<td></td>
</tr>
<tr>
<td>1 or 2 times</td>
<td></td>
</tr>
<tr>
<td>More than 6 times</td>
<td></td>
</tr>
<tr>
<td>3 or 4 times</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

**Over the last (timeframe TBC), how many times have you been to see a hospital doctor regarding pelvic pain or menstrual symptoms? Please tick one box only**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Ticking Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>5 or 6 times</td>
<td></td>
</tr>
<tr>
<td>1 or 2 times</td>
<td></td>
</tr>
<tr>
<td>More than 6 times</td>
<td></td>
</tr>
<tr>
<td>3 or 4 times</td>
<td></td>
</tr>
<tr>
<td>Do not know</td>
<td></td>
</tr>
</tbody>
</table>

If you have seen a hospital doctor, what did they say and treatment did you receive?

.................................................................

.................................................................

Have you had to take time off work because of your pelvic pain, menstrual symptoms or to attend healthcare services for treatment?

<table>
<thead>
<tr>
<th>Response</th>
<th>Ticking Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>if yes, how many days ______</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Have you had been admitted to hospital to have treatment for heavy menstrual bleeding or pelvic pain?

<table>
<thead>
<tr>
<th>Response</th>
<th>Ticking Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Have you had an operation for heavy menstrual bleeding or pelvic pain?
Yes
No

If yes, please write the name of the operation, or what you can remember about the operation here:
...........................................................................................................................................................................
...........................................................................................................................................................................

Have you regularly purchased medicines, such as pain killers, or anything else from the pharmacy to help with your menstrual symptoms or pains?
Yes
No

If yes, then please write down what you purchased here:
...........................................................................................................................................................................
...........................................................................................................................................................................
...........................................................................................................................................................................

How much money do you think you have spent on medications purchased for pelvic pain or menstrual symptoms?
Less than £10
£10-£20
£20-£40
£40-£60
More than £60