# Prevalence of pelvic vein thrombosis in women attending gynaecological outpatient clinics

**R&D REF: 14/0423**

**UCL DATA PROTECTION REGISTRATION REF: Z6364106/2014/08/09, SECTION 19**

# 1 Title page

## *1.1 Title*

Full title:

Prevalence of pelvic vein thrombosis in women attending gynaecological outpatient clinics: A prospective observational cross-sectional study

Short title:

Prevalence of pelvic vein thrombosis in women

## *1.2 Names, Roles, contact details*

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### *1.3 Protocol Details*

Version 3

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# 2 Signature Page

# 3 Contents



# 4 Abbreviations

COCP = combined oral contraceptive pill

GDOTU = Gynaecology Diagnostics and Outpatient Treatment Unit

POP = progestogen only pill

VTE = venous thromboembolism

DVT = deep vein thrombosis

PE = pulmonary embolism

TV US = transvaginal ultrasound

# 5 Summary of Research

Deep vein thrombosis is an important health problem. Recent studies have shown that a proportion of women attending for a gynaecological ultrasound scan have evidence of asymptomatic pelvic vein thrombosis. This is a novel observation and the clinical significance of this finding is unknown. The primary aim of our study is to establish the prevalence of asymptomatic pelvic vein thrombosis in the population of women attending gynaecological outpatient clinics. Our secondary objectives are to study the natural history of pelvic vein thrombosis and to identify factors which may contribute to their formation.

We are planning to conduct a prospective cross sectional observational study. We aim to recruit women who are referred to our gynaecological outpatient department for clinical assessment and ultrasound scans. In all women, in addition to the standard examination of pelvic organs, we will examine the pelvic veins and look for the signs of thrombosis. Those with evidence of blood clots in the pelvis will be offered a thrombophilia screen. Women with positive results will be then referred for haematological assessment. Those with negative thrombophilia screen will be followed up at one, three and six months following the initial diagnosis or until resolution is documented on the scan. Women with persistent clots after six months follow up will also be offered haematological assessment and advice. We aim to include 2574 women over 19 months.

# 6 Background

## *6.1 Literature review and justification*

Deep venous thrombosis (DVT) affecting lower limbs is a potentially serious medical disorder, which may cause pain and result in venous thromboembolism (VTE). This is more likely to occur in older women and other predisposing factors include prolonged immobility, infection, cancer

and surgery [1]. The risk of VTE is also increased in younger women who are pregnant and in those who are using the combined oral contraceptive pill (COCP). In the UK, pulmonary embolism remains a leading cause of direct maternal death during pregnancy. However, recent enquiry into maternal deaths in pregnancy showed a significant fall in the absolute number of deaths attributed to VTE form 33 in the triennium 2003-2005 to 16 in 2006–2008. This could be a results result of better recognition of at-risk women and more widespread use of thromboprophylaxis. The risk of VTE in women taking COCP has been estimated at 50 - 100/100,000 women years, which represents up to a 10 - fold increase over the background risk[2]. Women with congenital or acquired thrombophilia are also at increased risk of developing VTE[3].

Compression ultrasound (CUS) is a standard test for the diagnosis of DVT of the lower limb. The diagnostic technique was developed over 20 years ago[4] and involves applying gentle pressure on the veins of the limb using the ultrasound probe. Inability to compress a vein indicates the presence of DVT[5]. Other signs of DVT on ultrasound are venous dilatation, intraluminal echogenicity and absence of colour flow signals on Doppler examination[6]. It has been shown that CUS has a sensitivity of 97.5% for the diagnosis of deep vein thrombosis and it has largely superseded contrast venography as the investigation of choice[7].

Women may also develop isolated pelvic vein thrombosis which is considered to be rare in non – pregnant women [8, 9]. It is also unknown whether risks associated with pelvic vein thrombosis are comparable to those with thrombosis affecting lower limbs. The diagnosis of pelvic vein thrombosis is difficult due to non - specific symptoms and is usually made only after the thrombus extends into the veins of the lower limb. Torkzad et al.[10] compared magnetic resonance angiography (MRA) to CUS for the diagnosis of deep – vein thrombosis. In their study, 3 out of 27 symptomatic pregnant women examined had a normal CUS but were found to have ileo-femoral thrombosis when examined within 72 hours by MRA[10].

In recent years an increasing number of women are having transvaginal ultrasound scans for a wide range of gynaecological indications. The pelvic veins are often examined in women presenting with pelvic pain to rule out pelvic congestion syndrome. However, there is a paucity of data on the diagnosis and prevalence of incidental pelvic vein thrombosis in women. Recently we have published a first report in the literature describing ultrasound diagnosis of pelvic vein thrombosis in six asymptomatic non-pregnant women. Our data showed that pelvic vein thrombosis is not as rare as previously thought and that majority of women had identifiable pre-disposing factors for development of blood clots. Although the diagnosis of pelvic vein

thrombosis on ultrasound is relatively simple the natural history, clinical significance and optimum management strategy are unknown.

# 7 Aims and Objectives

The primary aim of the study is to determine the prevalence of pelvic vein thrombosis in women attending gynaecology outpatient clinic. The secondary outcomes are: natural history and identification of factors contributing to clot formation.

# 8 Study Design

## *8.1 Design Summary*

This will be a prospective observational cross-sectional study.

# 9 Study Group

Women referred for gynaecological assessment who consent to take a part in the study will be the subjects.

Our population will be sourced from the following referral pathways:

- GP
- Internal hospital referrals

## *9.1 Centres participating*

- Gynaecology Diagnostic and Outpatient Treatment Unit, Elizabeth Garrett Anderson Wing, University College Hospital

## *9.2 Inclusion Criteria*

- Women aged 18 and over attending gynaecology outpatient clinics

- Signed written consent
- Ability to tolerate transvaginal scan
- Women found to have a pelvic vein clot on transvaginal scan

### *9.3 Exclusion Criteria*

- Inability to tolerate transvaginal scan
- Severe pelvic pain

### *9.4 Eligibility*

All women booked for pelvic ultrasound examination will be sent a study information sheet with their appointment letter. Those who meet the inclusion criteria and provide written consent will be recruited into the study.

## 10 Recruitment of Participants

### *10.1 Method of recruitment*

Patients will be recruited at the time of attendance at the gynaecology outpatient clinic. All women referred to the gynaecological outpatient clinic will have a patient information leaflet sent with their appointment letter. At their gynaecology appointment, those women who have read the study information and meet the inclusion criteria will be asked to sign a consent form prior to the scan (see Appendix). Patients will be informed that there will no personal identifiable details recorded if they are recruited. Those women who do not wish to take part in the study will have their transvaginal scan as per routine practice and their care will be unaffected.

Hospital trust translators are used if there is a language barrier as standard practice. The patient's GP will be notified of the findings and participation into the study if the participant consents to this.

### *10.2 Subject Stipends or Payments*

None

### *10.3 Study Timetable*

Recruitment will run between the 1st January 2015 to 31st August 2016.

# 11 Data Collection

The data source will be from the history taken and ultrasound scan performed during the consultation, which is recorded onto a secure NHS database (Viewpoint). Although this is usual standard care, the clinical data will be included as part of the research study. Information about the ultrasound findings will be collected at the initial consultation and at the follow up scan appointments if there is a pelvic vein thrombus at four weeks, three months and six months by the student involved in this study (Dr Tejal Amin, EGA wing, UCLH).

The following data will be collected at the time of consultation and scan: anonymous demographic information (age, BMI, ethnicity, smoking history); obstetric history (gravida, parity, pregnancy outcome, type of delivery, uterine instrumentation in pregnancy, instrumentation of uterus outside pregnancy); gynaecological history (age of menarche, number of days of menstruation, menorrhagia, dysmenorrhea, dyschezia, breastfeeding history, use of COCP or POP, use of coils); past medical history (cancer, varicose veins, recent surgery); ultrasound findings (uterine shape/anomaly, presence of adenomyosis, presence of fibroids/mass and size, ovarian volume, adnexal mass, maximum uterine vein diameter, blood flow velocity, flow rate, presence of clot, size of clot at initial scan and then at follow up at one, three and six months); thrombophilia screening results. Please see appendix 20.3 for a full data set.

The data will be entered into a spreadsheet (Microsoft Excel version 14.0) (see appendix 20.3).

# 12 Data Handling and Record Keeping

## *12.1 Confidentiality and Security*

All patient records will be handled according to NHS confidentiality practices. Patient identifiable data will not leave NHS hospital premises. Anonymised hard copies of patient clinical letters will be placed in a dedicated file which will be kept in a locked cabinet in the clinic office.

## *12.2 Data transfer*

Anonymous clinical data will be collected from patients in accordance with the patient consent, patient information sheet and section 11 of this protocol. The anonymous clinical data will be available to Dr Tejal Amin (student) and Mr. Davor Jurkovic (Chief Investigator) for statistical

analysis. Mr. Davor Jurkovic will act as the data controller of such data for the study. Dr Tejal Amin will process, store and dispose of the anonymous demographic data, ultrasound findings and thrombophilia results in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. All data information will be anonymised and stored on encrypted NHS drives.

### *12.3 Intellectual Property Rights*

All background intellectual property rights (including licenses) and know-how used in connection with the study shall remain the property of the party introducing the same and the exercise of such rights for purposes of the study shall not infringe any third party's rights.

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site shall belong to UCL.

Nothing in this section shall be construed so as to prevent or hinder the participating site from using know-how gained during the performance of the study in the furtherance of its normal activities of providing or commissioning clinical services, teaching and research to the extent that such use does not result in the disclosure or misuse of confidential information or the infringement of an intellectual property right of UCL. This does not permit the disclosure of any of the results of the study, all of which remain confidential.

### *12.4 Archiving*

Any data generated during the study in non-identifiable format may be retained indefinitely by the student. All identifiable data will be purged at the end of the research.

## 13 Study Procedures

### *13.1 History taking*

The first step of the study will be to obtain a full history from the patient. This is part of routine clinical practice for all patients who present to the gynaecology outpatient clinic. The information elicited from the history that will be included has been referred to in section 11 (see appendix 20.3).

## *13.2 Procedure for transvaginal ultrasound*

### 13.2.1 Routine transvaginal ultrasound of pelvic organs

Women referred to our gynaecology clinic at University College Hospital are assessed by gynaecologists trained in transvaginal ultrasonography. Before the examination, a full history is taken and entered in a secure NHS clinical database (Viewpoint). All women with symptoms of gynaecological disease undergo a transvaginal scan as part of a routine assessment. The examination is performed systematically in the following manner: first the uterus is examined in the transverse plane to identify the cervical canal, the uterine cavity and both interstitial portions of the fallopian tubes. Acquired uterine anomalies, such as fibroids or adenomyosis, are diagnosed based on direct visualization using previously described diagnostic criteria[12,13]. Once the examination of the uterus is completed, the ovaries and the adnexae are also examined. The presence of any abnormalities in the ovaries or the adnexa is documented. If a significant abnormality, such as suspected neoplasm, is detected a senior member of the team is asked to repeat the examination to confirm the findings.

### 13.2.2 Examination of the pelvic veins for research protocol

Following the completion of the assessment of the pelvic organs, we will examine the pelvic veins for the presence of blood clots. The veins will be identified lateral to the uterus and followed within the broad ligament until they reach the point where they drain into internal iliac veins. The maximum diameter of the largest vein will be recorded in the transverse plane. Flow velocity studies will be performed using Doppler ultrasound with and without the Valsalva manoeuvre.

Diagnosis of pelvic vein thrombosis will be made in women with evidence of single or multiple well-defined echogenic lesions within the lumen of pelvic veins causing a partial or complete obstruction to blood flow on colour Doppler examination[6]. In all cases the diagnosis will be confirmed by a senior clinician. If the diagnosis is confirmed the thrombi will be measured in 3 orthogonal planes and the diameters will be recorded. These results will compared to the findings on subsequent follow up scans.

## *13.3 Procedure for women diagnosed with pelvic vein thrombosis*

Women diagnosed with pelvic vein thrombi will be advised about the uncertainty regarding clinical significance of this condition. They will be offered a full thrombophilia screen on the day of diagnosis. Those with abnormal results of blood tests will be contacted immediately and referred to a consultant haematologist for review and advice regarding further investigations and management. Women with negative thrombophilia screen will be offered another scan one month later to check for the resolution of the blood clot. Those with persistent clots will be seen again three and six months later. If at any point patients are concerned about the diagnosis or have queries they will be referred for haematological consultation. Those with persistent blood clots at the six month visit will also be offered an appointment with the consultant haematologist to discuss further management.

### 13.3.1 Ethical Considerations

Natural history and clinical significance of incidentally diagnosed pelvic vein thrombosis is uncertain. In standard clinical practice deep vein thrombosis is typically diagnosed in symptomatic women who are routinely offered treatment with anticoagulants. Although this policy is appropriate for women with leg thrombosis there is some evidence that pelvic vein thrombosis follows more benign clinical course with a majority of clots resolving spontaneously without causing any clinical symptoms. Symptomatic and asymptomatic deep venous thrombosis can often lead to long-term venous dysfunction with the development of post-thrombotic syndrome. Animal studies have demonstrated that thrombi forming under reduced flow conditions are less likely to resolve spontaneously which can lead to fibrosis-mediated remodeling of the vessel wall [(18)]. Deatrick et al [(19)] conveyed that even if there is resolution of the thrombus, the vein wall is often thicker, reflecting scarring, chronic thrombus adherence and fibrosis. These are often seen as phelboliths, which are calcified foci within a vein wall. They are visible on plain radiograph, ultrasound and CT as hyperechoic lesions in 42-45% of women [(15, 16)], implying that the prevalence for asymptomatic venous thrombosis may be higher than previously thought.

Success of treatment of pelvic vein thrombosis is uncertain and our initial data shows that thrombi may recur after the treatment is stopped, with no evidence of embolism. In these cases women tend to be offered life-long anticoagulation which is associated with significant physical and psychological morbidity. In the absence of any data on the natural history of pelvic vein

thrombosis counselling of women is very difficult and arbitrary. Our study will provide for the first time information about natural history of pelvic vein thrombosis which is the first and essential step in the process of developing rational, evidence based approach to difficult clinical problems. Diagnosis of pelvic vein thrombosis in the majority of reported cases leads to treatment with anticoagulation under the guidance of haematologists. Although anticoagulation with low molecular weight heparin or warfarin is a recognized and safe treatment it can be associated with side effects, particularly when given over a prolonged period of time.

Risks and Benefits:
The risk of overtreatment is described in 13.3.1. The main benefit for participants is that screening for asymptomatic pelvic vein thrombosis may help to understand this condition better and to provide them and other women with evidence based treatment to this rare and complex problem.

# 14 Statistical Plan

This study will follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) methodology for observational studies[14]. It comprises of a checklist of 22 items to ensure accurate data collection, analysis and reporting (see appendix 20.4).

## *14.1 Sample Size Determination and Power*

We aim to screen 2574 eligible participants over 2 years. The prevalence of this condition is unknown but our initial experience indicates that it may be around 5/1000 women and the sample size has been calculated on this proportion [(17)].

## *14.2 Statistical Methods:*

We will perform multivariate logistic regression analysis to identify factors which may be contributing to asymptomatic pelvic vein thrombosis.

# 15 Compliance

## *15.1 Subject Compliance:*

Patients who do not have a pelvic vein thrombus will not be followed up in the study. Those with a thrombus will have scheduled follow up appointments at one, three and six, months. If there is evidence of clot resolution at the first or second visit, no further follow up will be arranged. Women who fail to attend for their appointments, will be contacted by telephone and will be offered another date for the follow up visit.

## *15.2 Withdrawal of subjects:*

Patients will have the opportunity to withdraw from the study at any point in the study period. Patients will be asked if the data collected upto the point of withdrawal can be used in the final analysis.

# 16 Study Administration

## *16.1 Organization and Participating Centers*

Patients will be recruited from gynaecology outpatients' clinic at University College London Hospital.

## *16.2 Funding Source and Conflicts of Interest*

None

## *16.3 Sponsorship*

We will be requesting sponsorship from the Joint Research Office at UCL.

# 17 Publication Plan

We will publish the results of our study in a thesis for a post-graduate doctorate qualification (MD) and international peer reviewed journals.

# 18 Reporting Serious Unexpected Adverse Events

All Serious Unexpected Adverse Events to a research subject in the study must be reported immediately to the sponsor using the following email address research-incidents@ucl.ac.uk.

A Serious Adverse Event

- Results in death
- Is life Threatening
- Requires Hospitalisation or prolongation of hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Any other serious medical occurrence

Serious Adverse Events will be documented from the point of enrolment until the patient is exited from study. Information recorded and reported shall include

- A description of the event
- The date of event onset
- The relatedness of the event to the procedure
- The expectedness of the event
- The outcome of the event
- The date the event was first noticed by, or reported to the investigator

All ongoing Serious Adverse Events will be followed-up until the last study visit.

Reporting Incidents

All incidents must be reported through the appropriate Trust incidents reporting system. Where the study is being conducted at UCLH then the incidents should be reported through Datix.

An incident in a research study is

- Something that should not have happened OR
- Something that should have happened but didn't

which significantly effects any of the following

- the rights and well being of the research subject
- the scientific value of the study
- the compliance of the study with all relevant legal rules or ethics guidance including the Data Protection Act and the Human Tissue Act.

# 19 University College London indemnity statement

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

# 20 Appendix

## *20.1 Patient information leaflet*

## *20.2 Patient consent form*

## *20.3 Data collection database*

## *20.4 STROBE checklist*

| | Item No: Ref in protocol | Recommendation |
|---|---|---|
| **Title and abstract** | 1: **1.1** | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2: **6.1** | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3: **7** | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4: **8** | Present key elements of study design early in the paper |

| | | |
|---|---|---|
| Setting | 5: **9,10.4,11** | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6: **9.1, 10** | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants |
| Variables | 7: **11, 13.2.2.1** | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8: **9,10,11** | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9: | Describe any efforts to address potential sources of bias |
| Study size | 10: **14.1** | Explain how the study size was arrived at |
| Quantitative variables | 11: **14** | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12: **14** | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13 | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data | 14: **11** | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| Outcome data | 15: **11** | Report numbers of outcome events or summary measures |

| | | |
|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalizability | 21 | Discuss the generalizability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

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