Retrospective review of the incidence of venous thromboembolism in pregnancy and the puerperium and identification of presenting complaints of pregnancy-related venous thromboembolism at Groote Schuur Maternity Centre, Cape Town between 1 January 2016 and 31 December 2016

University of Cape Town

MMED DISSERTATION

Dr. Colin Jaco Montgomery
MNTCOL001
Department of Obstetrics and Gynaecology
University of Cape Town

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University of Cape Town

Investigator

Dr. CJ Montgomery

MBChB (UFS)

Registrar

Department of Obstetrics and Gynaecology

University of Cape Town

Supervisor

Dr. LK Schoeman

MBChB, FCOG (SA), MMED (O+G)

Maternity Centre Senior Specialist

Department of Obstetrics and Gynaecology

University of Cape Town

Declaration

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Colin Jaco Montgomery

MNTCOL001

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Abstract

Background: Venous thromboembolism is one of the leading causes of morbidity and mortality around the world. In addition to the immediate morbidity, there is significant implications on delivery plans, future options of contraception and thromboprophylaxis in subsequent pregnancies. At present, no pre-test probability assessments are being used to predict venous thromboembolism in pregnancy. This is the first study in South-Africa, addressing venous thromboembolism in the perinatal period which specifically examines the epidemiology and clinical presentation in pregnancy and the post-partum period.

Objectives: To determine the incidence of venous thromboembolism in Groote Schuur Maternity Centre and to identify specific variables in the clinical presentation that had a predictive value of a thromboembolic event.

Methods: A quantitative, retrospective study with a descriptive comparative research design, for a twelve-month period from January 2016 to December 2016. All pregnant and postpartum patients who were sent for a venous duplex ultrasound, ventilation perfusion study or computerized tomography pulmonary angiogram from the Groote Schuur Maternity center were included. A folder review was conducted and the diagnosis and clinical presentation of all the patients were documented and analyzed. Incidence of VTE were estimated as the number of events per 1,000 deliveries. The number of hospital deliveries in 2016 were used as the denominator for calculating this incidence.

Results: A total of 41 (0.12%) patients had a venous thromboembolism. Six patients had a deep venous thrombosis (0.02%) and 37 had a pulmonary embolism (0.11%). Among the 186 retrieved medical records, 11 (28%) of the diagnosis occurred in the puerperal period and 28 (72%) during pregnancy. Among the 28 events during pregnancy, one (3%) was in the first trimester, nine (23%) in the second trimester and 18 (46%) in the third trimester. The majority of confirmed pulmonary emboli (72.22%) and deep venous thrombosis (66.67%) were diagnosed during the third trimester in pregnancy.

Among individuals with deep venous thrombosis, the most frequently reported symptoms and signs were leg pain (66.7%), leg swelling (66.7%) and tachycardia (66.7%). Patients without deep venous thrombosis presented more with leg swelling (76.3%), red discolouration (10.5%) and cellulites (10.5%). The only presenting clinical features that were significantly different were haemoptysis (p=0.01) and coughing (p=0.03).

Among those individuals without pulmonary embolus, tachycardia (77.3%) and dyspnoea (49.1%) were commonly reported. Among the patients with a PE, the most frequently reported symptoms were tachypnoea (78.4%), dyspnoea (64.9%), tachycardia (62.2%), chest pain

(51.4%) and coughing (46%). Features in the clinical presentation that were statistically significant were chest pain (p=0.01), haemoptysis (p=0.07), tachypnoea (p=0.01) and tachycardia (p=0.03). The greatest statistically significant clinical feature was the symptom of coughing (p<0.01). The stepwise logistic regression for the univariate analysis showed that coughing (OR=3.83; 95% CI: 1.71 to 8.58; P<0.01), chest pain (OR=2.57; 95% CI: 1.2-5.53; P=0.02), tachycardia (OR=1.03; 95% CI: 1.0 to 1.06; P=0.03), tachypnoea (OR=1.06; 95% CI: 1.0 to 1.12; P=0.05) and a median symptom of 3.5 (1.58; 95% CI: 1.23 to 2.06; P<0.01) were the best explanatory variables. The stepwise logistic regression for the multivariate analysis showed that both tachycardia (OR=1.03; 95% CI: 1.0 to 1.06; P=0.03) and coughing (OR=3.43; 95% CI: 0.88 to 11.30; P=0.05) predicted a positive pulmonary embolus.

A logistic regression for tachycardia showed a 23% increase in pulmonary embolus for every increase of 5 beats per minute in the heart rate above 100Bpm. This association was statistically significant (OR=1.23; 95% CI:1.08 to 1.39; P=0.0004)

A logistic regression analysis of the association between tachycardia, tachypnoea and chest pain and the risk of having a pulmonary embolus showed a 4% increase in the risk of pulmonary embolus for every single unit increase in heart rate. When controlling for tachycardia and tachypnoea, chest pain was also associated with a 3.8 times increase in the odds of having a pulmonary embolus. This association was statistically significant (p=0.0002)

Conclusion: In this study, we found that the incidence of venous thromboembolism in the Groote Schuur Maternity Centre was the same as in other developed and developing countries around the world. The majority of confirmed venous thromboembolisms were diagnosed during the third trimester in pregnancy. This study found a lower incidence of deep venous thrombosis in comparison to other studies. The clinical features that had some predictive value for pulmonary embolism were chest pain, coughing, tachypnoea, tachycardia and more than three symptoms or signs. Tachycardia was significant in the univariate-, multivariate analysis and stepwise logistic regression. In addition, there was a statistically significant association between tachycardia, tachypnoea and chest pain and the risk of having a pulmonary embolus. This study has revealed the need to develop pre-assessment algorithms in pregnancy and postpartum patients to reduce maternal and fetal, morbidity and mortality. Until such algorithms are developed, clinicians should use their own clinical judgment and proceed to diagnostic imaging for suspected VTE, where indicated.

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List of Acronyms

ART	Assisted Reproductive Technology
BMI	Body Mass Index
bpm	Breaths per minute
Bpm	Beats per minute
CS	Caesarean Section
CTPA	Chest Computerized Tomography Pulmonary Angiogram
DVT	Deep Venous Thrombosis
GSH	Groote Schuur Hospital
IVF	In Vitro Fertilization
ICD	International Statistical Classification of Disease and Related Health Problems
kPa	Kilopascal
LMWH	Low Molecular Weight Heparin
MOU	Midwife Obstetric Units
mmHg	Millimetre of Mercury
OD	Odds Ratio
PE	Pulmonary Embolus
P-value	Calculated Probability
SLE	Systemic Lupus Erythematosus
RCOG	Royal College of Obstetrics & Gynaecology
UFH	Unfractionated Heparin
UK	United Kingdom
USA	United States of America
V/Q	Ventilation/Perfusion
vs	Versus
VTE	Venous Thromboembolism

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Definitions

Antepartum period

Date of conception to the date of delivery. For woman without the recorded information on the gestational age of the baby at delivery, we defined the antepartum period as the nine months prior to date of delivery.

Hypoxia

Arterial partial oxygen level of less than 80mmHg or 10,6kPa on arterial blood gas.

Hypoxemia

Saturation of less than ninety present on an arterial blood gas or pulse oximeter.

Postpartum period

The period following delivery till the patient was discharged from the Groote Schuur Maternity Centre.

Tachycardia

Heart rate over 100 beats per minute.

Tachypnoea

Respiratory rate above 20 per minute.

Introduction

It was the 19th century German pathologist Rudolf Virchow, who first hypothesised that pulmonary embolism (PE) and deep venous thrombosis (DVT) are both manifestations of a single disease entity called venous thromboembolism (VTE). A century later, it is still a serious and potentially fatal condition and remains an important cause of maternal mortality and morbidity. According to the South African Saving Mothers Report, obstetrical thromboembolism was responsible for 2.7% of direct maternal deaths in 2014.[1]

Treatment and prevention of obstetric-related VTE is complicated by the need to consider fetal, as well as maternal, wellbeing when making management decisions.[2] Multiple studies have been done around the world to look at the epidemiology and risk factors of VTE in pregnancy. Currently there are no studies available looking at the epidemiology of VTE in pregnancy and postpartum, in South Africa or the African continent.

Many of the classical signs and symptoms of VTE can be associated with normal pregnancy and changes with advancing gestation. This makes the diagnosis of VTE extremely difficult and sometimes a diagnostic dilemma. No pre-test probability assessment has been validated for pregnant patients with a suspected VTE. This study aimed to look at the symptoms and signs patients presented with to improve this diagnostic predicament.

Peripartum haemorrhage is a leading cause of maternal mortality in the developing world, reflecting the haemostatic challenges and changes associated with childbirth. The maternal hypercoagulable state is a physiological preparation for delivery, creating a protective mechanism against maternal haemorrhage. This hypercoagulability state causes an increased risk of VTE in pregnancy and the postpartum period.[3]

Definition

Venous thrombosis is defined as the process of clot (thrombus) formation within veins. Although this can occur in any venous system, the predominant clinical events occur in the vessels of the lower limbs, giving rise to DVT, or in the lungs, resulting in a PE. Collectively referred to as VTE. [4, 5]

Epidemiology

In the developed world VTE is a leading cause of maternal death, in comparison to South Africa where non-pregnancy related infections are the leading cause. According to the South African Saving Mothers Report, pregnancy-related thromboembolism was responsible for 2.7% of direct maternal deaths in 2014.[1] Current estimates of deaths from pulmonary embolisms are 1.1 to 1.5 per 100,000 deliveries in the United States and Europe. In the United Kingdom, venous thromboembolism accounts for one third of all maternal deaths. Delayed diagnosis, delayed or inadequate treatment, and inadequate thromboprophylaxis contributed too many of these deaths.[6, 7]

During pregnancy, woman have a four- to five-fold increased risk of thrombosis, compared to when they are not pregnant.[8, 9] This is increased further in the postpartum period,[9-11] although the absolute risk is low with an overall incidence of VTE in pregnancy and the puerperium of 1-2 per 1,000 woman.[8, 12-17]

Multiple studies have been done over the world investigating the incidence and risk factors of VTE in pregnancy. The studies were mostly retrospective and used data bases and ICD 10 codes. The absolute incidence of VTE in pregnancy and the puerperium is 107 per 100,000 person-years in the UK,[10] 114 per 100,000 deliveries in Australia,[18] 175 per 100,000 pregnancies in Canada,[16] 172 per 100,000 deliveries in the USA,[19] 188 in 100,000 deliveries in China,[20] 125 in 100,000 deliveries in Saudi Arabia,[21] 107 per 100,000 pregnancy-years during pregnancy and 175 per 100,000 puerperal-years during the puerperium in Denmark.[17] There was one study done at GSH Maternity centre in 2005 that showed an incidence of 5.5 per 100,000 deliveries[22]. This study only looked at the diagnosis of new VTE in pregnancy.

This is lower than the incidence around the world. Currently there is new information needed in South Africa and the African continent about the epidemiology of pregnancy related thromboembolic disease.

Physiology

Virchow's Triad has formed the basis for understanding the pathogenesis of VTE. The three elements are venous stasis, changes in the vessel wall and changes in the composition of the blood. Pregnancy affects all three factors and likely explains the increased risk of VTE during pregnancy.[23]

Firstly, progestogen-mediated changes to the blood vessels that cause venous stasis, which begins by the end of the first trimester and is greatest at 36 weeks. Compression of the pelvic veins by the growing uterus adds to this later in pregnancy and affects particularly the left side. Almost 90% of deep venous thrombosis (DVT) occur on the left side in pregnancy, compared to 55% in the non-pregnant state.[24, 25]

Secondly, delivery is associated with vascular injury and changes at the uteroplacental surface, which probably contributes to the increased risk of VTE in the immediate postpartum period. Forceps, vacuum extraction, or surgical delivery can exaggerate vascular intimal injury and amplify this phenomenon.[7]

Thirdly, clotting factors alter in pregnancy. There are increases in factors V and VIII and fibrinogen, with an acquired resistance to activated protein C (endogenous anticoagulant) and a reduction in its co-factor, protein S which all promote a pro-coagulant state. There are also increases in inhibitors of plasminogen activator, resulting in decreased fibrinolysis.[24]

Risk factors

There are many risk factors for VTE in pregnancy. Over the past several decades, increased incidences of overweight and obese pregnant women, and the increased caesarean rates, has had a major impact on the increasing risk factors that promotes VTE.[23] The RCOG guidelines categorise risk factors for VTE into pre-existing, obstetric and new onset/transient:

Pre-existing risk factors:[26]

- Previous VTE
- Thrombophilia
- Medical comorbidities e.g. cancer, active SLE, sickle cell disease etc.
- Age >35 years
- Obesity (BMI ≥ 30 kg/m2) either pre-pregnancy or in early pregnancy
- Parity ≥ 3

- Smoking
- Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema or skin changes)
- Paraplegia

Obstetric risk factors:[26]

- Multiple pregnancy
- Current pre-eclampsia
- CS
- Prolonged labour (>24hours)
- Mid-cavity or rotational operative delivery
- Stillbirth
- Preterm birth
- Postpartum haemorrhage (>1litre/ requiring transfusion)

New onset/transient:[26]

- Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum
- Hyperemesis, dehydration
- Ovarian hyperstimulation syndrome (1st trimester only) (ART, IVF)
- Admission or immobility (≥ 3 days bed rest)
- Current systemic infection (requiring intravenous antibiotics or admission to hospital)
- Long distance travel (>4 hours)

Symptoms and Signs

The majority of women with VTE during pregnancy have clinical symptoms. Many of the classical signs and symptoms can be associated with normal pregnancy and changes with advancing gestation.[7] It may present with symptoms of DVT or the symptom complex consistent with the occurrence of PE.[23]

The symptoms and signs of DVT include unilateral leg pain, swelling and tenderness. Most DVT cases present in the left leg. This is likely owing to the compressive effects on the left common iliac vein as it is crossed by the right common iliac artery. Isolated deep vein thrombosis in the common iliac vein is also thought to be higher in pregnancy compared with the non-pregnant women.[23]

Clinical signs such as warmth, redness, asymmetric increase in the diameter of the leg or thigh, oedema, and a palpable cord or thrombus may be present. The signs and symptoms

result from obstructed venous return and/or in combination with vascular inflammation. Clinical suspicion is heightened when calf pain is elicited on passive dorsiflexion of the foot (Homan sign).[23]

The symptoms of PE include dyspnoea, pleuritic chest pain and cough. Tachypnoea occurs in more than 90% of patients. Other clinical signs include tachycardia, atelectatic rales, haemoptysis, diaphoresis, friction rub, cyanosis, and the development of an accentuated second heart sound, gallop, or murmur. In cases of massive PE, defined as obstruction of more than 50% of the pulmonary circulation, hypotension, syncope, or cardiovascular collapse may be the presenting features.[23] A low-grade pyrexia and leucocytosis can also occur with VTE.[27]

Diagnosis

Clinical suspicion is critical for the diagnosis of VTE. Common strategies for predicting PE and DVT have not been validated in pregnancy and there is no evidence to support the use of pre-test probability assessment, like the Wells score, in diagnosing VTE in pregnancy.[7, 27]

A major challenge in the diagnostic management of suspected PE is to reduce the number of false-negative and false-positive results. False-negative results are a concern because, according to studies conducted outside of pregnancy, untreated VTE, has a mortality rate as high as 30%, which falls to 8% if appropriately diagnosed and treated.[28, 29]

False-positive results in pregnant women will have implications on delivery plans, future options for contraception,[30] and thromboprophylaxis in subsequent pregnancies. Additionally women who are misdiagnosed with VTE will be given anticoagulation treatment, which is potentially associated with severe complications.[28]

Any woman with clinical features suggestive of VTE should have objective testing performed expeditiously and treatment with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). This should be given until the diagnosis is excluded by such testing, unless treatment is strongly contraindicated.[27]

Doppler flow studies with compression sonography are the primary non-invasive tests used in diagnosing DVT.[23] It involves gently pressing the vascular lumen with the ultrasound probe. A fully compressible vein indicates the absence of thrombosis. It also evaluates the blood flow characteristics with pulsed Doppler. Normal flow is phasic with respiration and an absence of this phasic pattern indicates venous outflow obstruction.[24]

If the ultrasound is negative and there is a low level of clinical suspicion, anticoagulant treatment may be discontinued. In the event that the ultrasound is negative and a high level of clinical suspicion exists, anticoagulant treatment should be discontinued but the ultrasound

repeated on days three and seven. If repeat testing is negative, no further treatment is required.[27]

Chan *et al* evaluated this strategy in a prospective cohort study of 221 pregnant women who presented with suspected DVT. The sensitivity of serial compression ultrasonography with Doppler imaging was 94.1%, the negative predictive value was 99.5% and the negative likelihood ratio was 0.068.[31]

Like DVT, the diagnosis of PE is difficult to confirm on clinical grounds alone. Diagnostic tests must be used to dictate management in cases of suspected PE. Patients with suspected PE and normal findings on compression ultrasound must undergo additional diagnostic tests.[24] These test include chest X-ray, electrocardiogram and arterial blood gas. These diagnostic adjuncts are of limited value for the diagnosis of suspected PE in non-pregnant and pregnant patients, but can be used to rule out other diagnoses for the patient's symptoms.[32-35]

D-dimers are derivatives of fibrin, produced by plasmin degradation, and several assays are available to measure circulating levels. In the non-pregnant patient, D-dimer testing is useful because of the high negative predictive value if the blood level is low. However, in pregnancy, there is a progressive rise in D-dimer levels with advancing gestation and levels become abnormal at term and in the postnatal period.[36, 37] A positive test is unhelpful and should not be performed in the investigation of acute VTE in pregnancy.

The cornerstone of diagnosing a PE is ventilation/perfusion (V/Q) scan, though in many places spiral computed tomography is now the first line imaging technique to diagnose a PE in a non-pregnant patient.[38] Technetium (99 mTc) labelled albumin microspheres injected intravenously are trapped in the pulmonary capillary bed thus, accurately depicting the distribution of pulmonary blood flow. The vascular perfusion scan is coupled to a ventilation scan to enhance overall specificity.[23] In pregnancy, pulmonary scintigraphy dose reduction may be achieved by reducing the dose of the perfusion agent (by 50–75%) and reducing or eliminating the ventilation component (performing perfusion scintigraphy).[39]

The Prospective Investigation of Pulmonary Embolism Diagnosis was a large, prospective, multicentre trial that examined the diagnostic use of the ventilation-perfusion scan. Eighty-eight percent of patients with a high-probability scan had angiographic evidence of PE. The study also showed that the combination of clinical assessment and the ventilation-perfusion scan improved diagnostic accuracy. The diagnosis of PE was accurate in patients with a high clinical suspicion and where the VQ scan reported a high probability of PE. A normal or near normal scan or a low-probability scan in a patient with low-clinical suspicion excluded the diagnosis of PE. Indeterminate scans or low probability scans with high clinical suspicion were not helpful in the diagnosis of PE.[40]

Studies have also compared V/Q or low-dose perfusion (Q) scans with CTPA for the detection of PE during pregnancy and have found comparable negative predictive values (99% and 100% for CTPA and VQ scans respectively) and no significant difference between the number of positive, non-diagnostic and normal scans.[41-43] V/Q scanning is the first-line investigation in most countries due to its marginally higher predictive value in diagnosing PE and its substantially lower radiation dose to pregnant breast tissue than CTPA.[44, 45] CTPA can identify other pathology including pneumonia, pulmonary oedema and aortic dissection.[42, 43] The RCOG guideline on the management of VTE suggests that if the chest X-ray is abnormal a CTPA should be performed in preference to a V/Q scan.[27]

Clinicians arranging imaging scans for suspected PE in pregnancy should be aware of the potential risks surrounding fetal and maternal radiation exposure.[46] CTPA exposes the fetus to similar or lower amounts of radiation as V/Q scanning, although studies have been confounded by the type and model of scanners used, the imaging protocols employed and the methods used to estimate radiation exposure.[28] With both techniques, the doses employed are well below accepted thresholds for teratogenicity, fetal death and fetal growth restriction. The main concern for the fetus is the minimal risk of childhood cancer.[47] The International Commission on Radiological Protection has estimated an increased risk of fetal childhood cancer to the age of 15 following in utero radiation exposure of 0.006% per mGy, which equates to a risk of 1 in 17,000 per mGy.[48] The fetal radiation exposure associated with CTPA and V/Q is approximately 0.1 mGy and 0.5 mGy respectively, although quoted figures vary considerably.[47, 49, 50]

While CTPA is associated with a lower risk of radiation for the fetus than VQ scan, this must be offset by the relatively high radiation dose (up to 20 mGy) to the mother's breast tissue, which is associated with an increased risk of breast cancer. The dose estimate for CTPA is 20 to 100 times greater than for V/Q scanning. The radiation dose depends on breast size, the technique used and the age of the woman.[51]

The choice of technique for definitive diagnosis of suspected PE (V/Q scan or CTPA) will depend on local availability. Hospitals should have an evidence-based protocol for the objective diagnosis during pregnancy.[27] Where feasible, women should be involved in the decision to undergo CTPA or V/Q scanning. Ideally, informed consent should be obtained before these tests are undertaken due to the fetal and maternal risks posed by either modality.[26]

Treatment

Acute treatment for VTE during pregnancy and the puerperium includes prompt therapeutic anticoagulation with intravenous heparin, supplemental oxygen in the case of PE, and coordinated multidisciplinary care in a tertiary care centre capable of dealing with the critical care implications for the mother, baby and cardiopulmonary complications.[23]

This management must be undertaken with extraordinary care and an in-depth understanding of maternal and fetal physiology and the effects of the therapy on both mother and fetus. Therapeutic considerations in pregnant women are quite different from non-pregnant patients. More importantly, knowledge of the effects of anticoagulation on the fetus before, during and after birth is critical. Health care providers need to be experienced in the concurrent management of VTE and common obstetric conditions. Anticoagulation can have serious implications when obstetric emergencies and/or unplanned delivery occur.[52]

Prophylaxis

Prophylaxis is recommended against venous thromboembolism in women with a history of prior thromboembolic episodes. Anticoagulation is also indicated for those women considered to be at risk because of the presence of an inherited or acquired thrombophilia. In patients who require therapeutic anticoagulation for a radiologically diagnosed VTE during the antenatal period, they will also generally require therapeutic anticoagulation during the postpartum period.[23]

Venous thrombosis during pregnancy and the postpartum period fortunately remain rare. However, the risk for morbidity and mortality remains significant.[23] Diagnostic imaging and therapeutic anticoagulation in conjunction with prolonged hospitalization, both increase the risk for the fetus and the mother. It is thus necessary to obtain more information about VTE in South Africa to determine its incidence, improved diagnostic parameters and reduce maternal and fetal risks related to over- and under diagnosis.

Aims and Objectives

Research question

What is the incidence of venous thromboembolism in pregnancy and the puerperium at Groote Schuur Maternity Centre, Cape Town between 1 January 2016 and 31 December 2016?

Hypothesis

The incidence of thromboembolic events at Groote Schuur Maternity Center is no different to other maternity centers and countries around the world.

Aims

The aim was to determine the incidence of venous thromboembolism in pregnancy and the puerperium at Groote Schuur Maternity Centre, Cape Town between 1 January 2016 and 31 December 2016

Objectives

Primary objectives:

- To determine the incidence of venous thromboembolism in this study population
- To compare the incidence of venous thromboembolic events at this institution to that of other studies and data bases around the world

Secondary objectives:

- To identify presenting signs and symptoms of patients that had a radiological confirmation of a thromboembolic event
- Statistical analysis of presenting signs and symptoms to identify which clinical features are positive predictors of VTE

Study Methods

Study Design

A quantitative, retrospective study with a descriptive comparative research design, for a twelve-month period from January 2016 to December 2016

Study Population

All pregnant and postpartum patients who were sent for a venous duplex ultrasound, ventilation perfusion study or computerized tomography pulmonary angiogram from the Groote Schuur Maternity Center, between 1 January 2016 and 31 December 2016, were included in this study.

The study was conducted at Groote Schuur Hospital in Cape Town, South Africa. Groote Schuur Hospital is a Tertiary Level Hospital providing obstetric and neonatal services to a large drainage area in the Western Cape.

The hospital receives referrals from multiple Midwife Obstetric Units (Mitchells Plain, Gugulethu, Retreat, Hanover Park, Vanguard MOU's), Level 1 Hospitals (Mitchells Plain District, West fleur, Vredenburg, False Bay Hospitals) as well as Level 2 Hospitals (Mowbray Maternity and New Somerset Hospital). All medical problems that complicate pregnancy are referred to the obstetric service at Groote Schuur Hospital. On rare occasions, patients might be referred from one of the several private hospitals in the surrounding areas.

The exclusion criteria for this study were:

- Patients that have already been diagnosed with a radiologically confirmed thromboembolic event at any other unit or referring hospitals outside of the GSH maternity center
- Any patients that has been diagnosed with a thromboembolic event at post mortem

Data collection

- All the patients undergoing a VQ scan while admitted to the Groote Schuur Maternity Center was identified by the Nuclear Medicine Registers. The reports were downloaded from the Nuclear Medicine Database and documented if there was a radiological evidence of a PE.
- All patients that were sent for a Venous Duplex Doppler and CTPA were registered on the GSH PACS system. By inserting a code in advance search, patients can be identified and radiological evidence of a VTE was documented.

- All the data that was gathered from the Nuclear Medicine registers and the GSH PACS were entered into an electronic spreadsheet (Microsoft Excel).
- A folder review was conducted of all the patients that were sent for radiological study to confirm a VTE. Relevant medical information was transferred to a specific case report form developed for this study. (See Appendix A)

The following data were extracted:

- Whether the clinical presentation was during the antenatal or postpartum period
- Trimester of pregnancy, if clinical presentation was antenatally
- Presenting symptoms and signs when a VTE was suspected

The following baseline signs and symptoms were analysed as potential predictors of a VTE: leg pain, leg swelling, red discolouration of lower limbs, increased warmth of lower limbs, cellulites, dyspnoea, chest pain, haemoptysis, syncope, dizziness, coughing, tachypnoea, tachycardia, hypoxia and hypoxemia

For the analysis, the signs and symptoms were analysed as either absent or present except tachypnoea, tachycardia, hypoxia and hypoxemia were the specific measurement was documented.

Sample size

The study was conducted over the course of one year period.

Based on a test sample from 01 October 2016 to 31 October 2016. Seventeen people were sent for a radiological investigation of a suspected thromboembolic event. Seven were diagnosed with a VTE.

Data analysis

Incidence of VTE were estimated as the number of events per 1,000 deliveries. The number of hospital deliveries in 2016 were used as the denominator for calculating the incidence. We calculated the incidence of VTE in the antepartum and postpartum periods as well as the incidence in each of the three antenatal trimesters. Symptoms of DVT and PE were identified form clinical records. Logistic regression, standard statistical tests and relationships were expressed using unadjusted and adjusted (for all covariates) odd ratios using 95% confidence intervals. Significance was set at the 5% level or p-value of less than 0.05. The results are presented in Figures and Tables.

Ethical considerations

The following ethical principles were adhered to during the course of this study:

Social value

VTE is a serious and potentially fatal condition and remains an important cause of maternal mortality and morbidity worldwide. This study aimed to measure the incidence in South Africa and to determine the symptom-complexes patients present with to improve our knowledge of this fatal disease.

Respect for patients

Data was collected retrospectively and there was no direct contact between the researcher and patients.

Privacy and confidentiality

All patient information were treated with confidentiality in accordance with the Declaration of Helsinki.[53]. All information/data collected was kept in a separate password protected file and this was only known to and accessed by the investigator. There were no risks for patients or medical personnel involved in the study.

Independent review

The protocol was approved by the Health Research Ethics Committee (HREC) of Cape Town University, with ethics approval number 822/2017. See Appendix B.

Informed consent

Informed consent was not required from the participants, as data were collected retrospectively from the registers, data bases and patient folders. There were minimal risks to the subjects involved and the study did not adversely affect the right and welfare of the subjects.

Collaborative partnerships

The researcher worked closely with their supervisor, advisors and stakeholders. Ethical principles, especially privacy and confidentiality, were strictly adhered to.

Dissemination of results

The results will be presented to the clinical units participating in this study. The results will further be presented to the Department of Obstetrics and Gynaecology at Groote Schuur Hospital.

The research study will be submitted in partial fulfilment of the requirements for the Master of Medicine degree of the University of Cape Town and the FCOG (SA) examination. The results will also be submitted for publication in an appropriate journal.

Declaration of interest

There are no conflicts of interest.

Budget

There were minimal costs involved in the execution of the study apart from basic stationary. The statistician was remunerated from the departmental research fund.

Results

Baseline Characteristics

During the period from 1 January 2016 to 31 December 2016, there were 198 patients with clinical suspicion of pregnancy associated thromboembolism. Figure 1 is a flow diagram of patients who met the inclusion criteria.

During the medical folder review, ten patients did not have all the medical information as needed on the folder review form. They were not excluded from the study. They were only excluded from the calculations of the specific parameter that was missing. All medical records of patients included in the study was available for data capture.

Among the 186 patients, 25 were sent for left leg Doppler (13.4%), 25 for right leg Doppler (13.4%), 118 patients for VQ scans (63.4%) and 31 patients for CTPA (16.7%). The majority of VTEs was diagnosed with a VQ scan. There were 13 patients who had more than one diagnostic imaging. Table 1 and 2 (refer to appendices) compared the differences between baseline characteristics between patients with a PE and PE workup, and patients with a DVT and DVT workup, respectively.

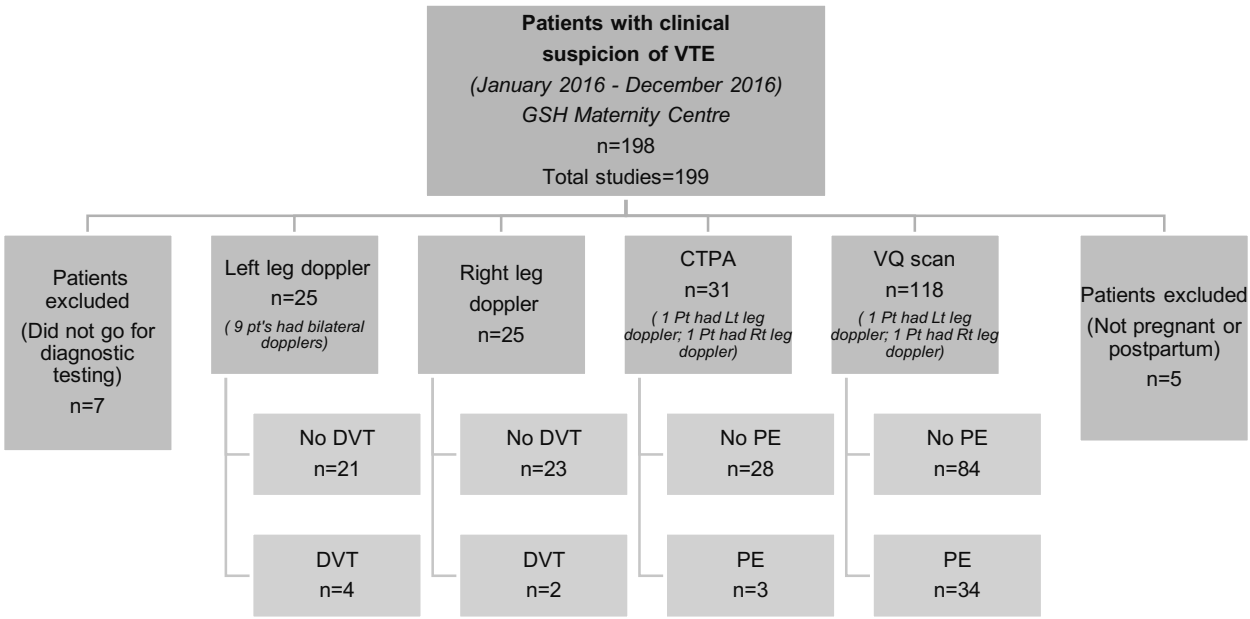

Figure 1: Baseline characteristics

Risk of VTE in pregnancy overall

During the period from 1 January 2016 to 31 December 2016, there were 33,503 deliveries in the Metro-west district. A total of 41 (0.12%) patients had a VTE, or 1,2 in 1 000 pregnancies. There were 6 incidents of DVT (0.02%) and 37 of PE (0.11%). Two patients had simultaneous DVT and PE at the time of diagnosis.

Risk by trimester and postpartum

Among the 186 retrieved medical records, 11 (28%) of the diagnosis occurred in the puerperal period and 28 (72%) during pregnancy. Among the 28 events during pregnancy, one (3%) was in the first trimester, nine (23%) in the second trimester, and 18 (46%) in the third trimester. The majority of confirmed PE's (72.22%) and DVT's (66.67%) were diagnosed during the third trimester in pregnancy. Figure 2 is an illustration of the VTE per trimester and the antenatal and postnatal period.

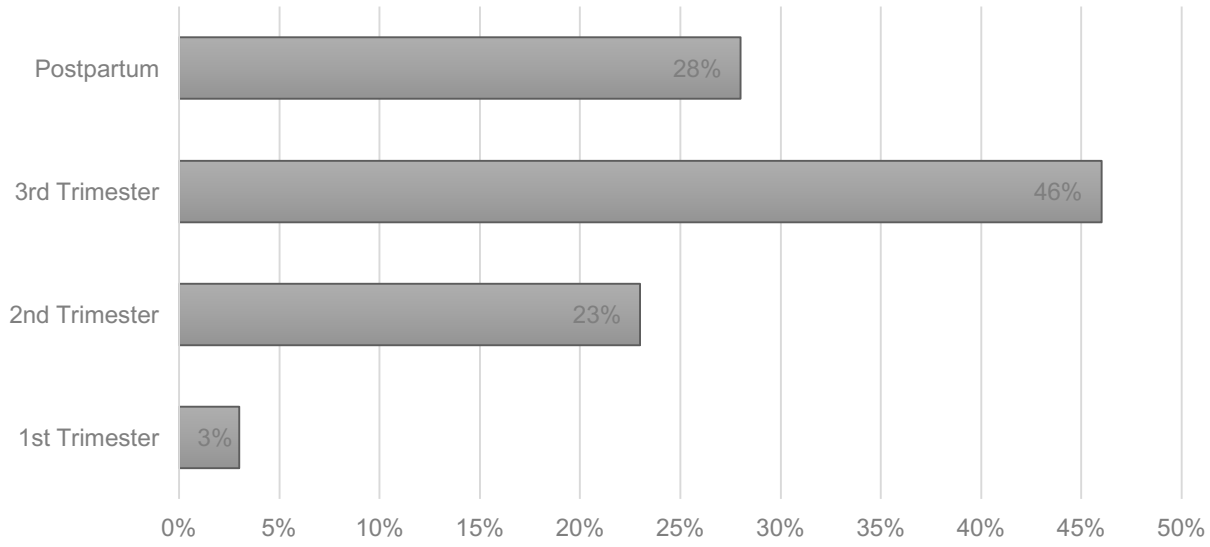

Figure 2: VTE per trimester

Monthly distribution of VTE and diagnostic studies

Figure 3 and 4 is an illustration of the monthly distribution of VTE diagnostic studies and radiologically confirmed VTEs. There were a total of 199 studies performed for patients with presumed VTE in the Groote Schuur Maternity block in 2016. February had the least studies with only eight and March had the most with 24 studies. There was a median of 16,6 studies per month.

The most PE's was diagnosed in April and the most DVTs was diagnosed in October.

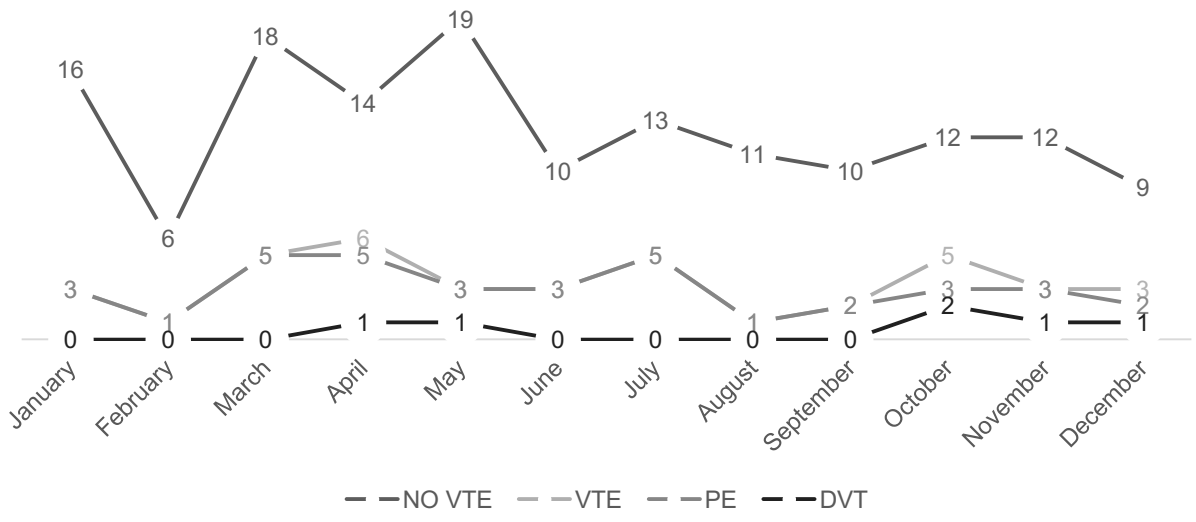

Figure 3: Monthly distribution of VTE

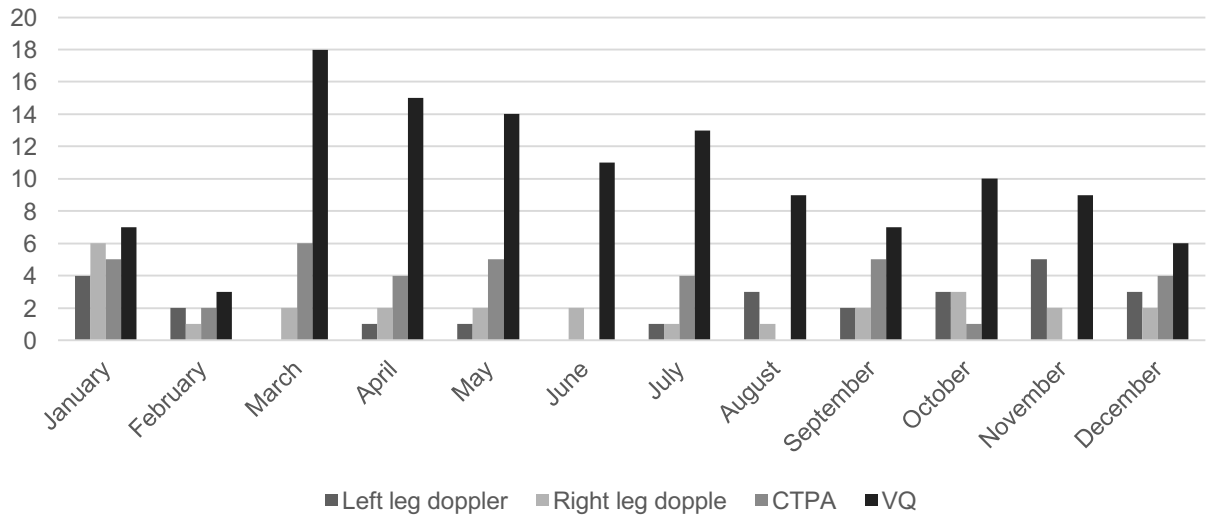

Figure 4: Monthly distribution of VTE diagnostic studies

Signs and Symptoms of DVT

Table 3 and 4 compared the differences between clinical presentation of the patients with a DVT and those without a DVT. Among individuals with DVT, the most frequently reported symptoms and signs were leg pain (66.7%), leg swelling (66.7%) and tachycardia (66.7%). Patients without DVT presented more with leg swelling (76.3%), red discolouration (10.5%) and cellulites (10.5%). The only presenting clinical features that were significantly different were haemoptysis (p=0.01) and coughing (p=0.03). According to Figure 5, patients with a DVT had a higher pulse rate [107Bpm (87 to 109Bpm)] compared to patients without a DVT

[93.5Bpm (82 to 104Bpm)]. The patients with DVT had more symptoms and signs compared to the patients without a DVT, but this was not statistically significant.

As listed in Table 7 the stepwise logistic regression for univariate analysis selected all the signs and symptoms into the model. The model tested the effect of the symptom or sign on the outcome in patients with a positive DVT. Coughing (OR=9; 95% CI: 0.98 to 82.50; P=0.05) was the only explanatory variable. The stepwise logistic regression for the multivariate analysis could not be done due to only one variable that was statistically significant.

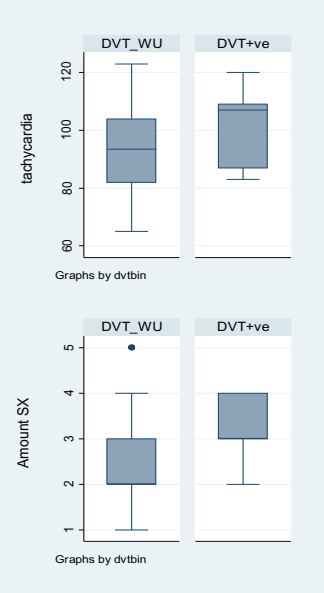

Figure 5: Box and whisker plot of DVT signs and symptoms

Signs and Symptoms of PE

Table 5 and 6 compared the differences between clinical presentation of patients with a PE and those without. Among the patients with a PE, the most frequently reported features on clinical presentation were tachypnoea (78.4%), dyspnoea (64.9%), tachycardia (62.2%), chest pain (51.4%) and coughing (46%). Among those individuals without pulmonary embolus, tachycardia (77.3%) and dyspnoea (49.1%) were also commonly reported. Individuals with pulmonary embolus were more likely than those without pulmonary embolus to have a baseline tachypnoea (78.4% vs 39%), dyspnoea (64.9% vs 49.1%), chest pain (51.4% vs 29.1%), coughing (46% vs 18.2%), hypoxia (21.6% vs 20%), hypoxemia (9.4% vs 7.3%), haemoptysis (98.1% vs 1.8%), dizziness (8.1% vs 4.6 %) and syncope (2.7% vs 1.8%).

The only clinical feature that was more prominent in patients without a pulmonary embolus was tachycardia (62.2% vs 77.3%) but the heartrate was higher with patients with a pulmonary embolus [120bpm (106 to 128bpm) vs 112(101 to 120bpm)]. The patients with pulmonary embolism who presented with tachypnoea also had a higher respiratory rate [24bpm (19 to

29bpm) vs 20 (18 to 24bpm)] than those without a pulmonary embolus. This is illustrated in Figure 6.

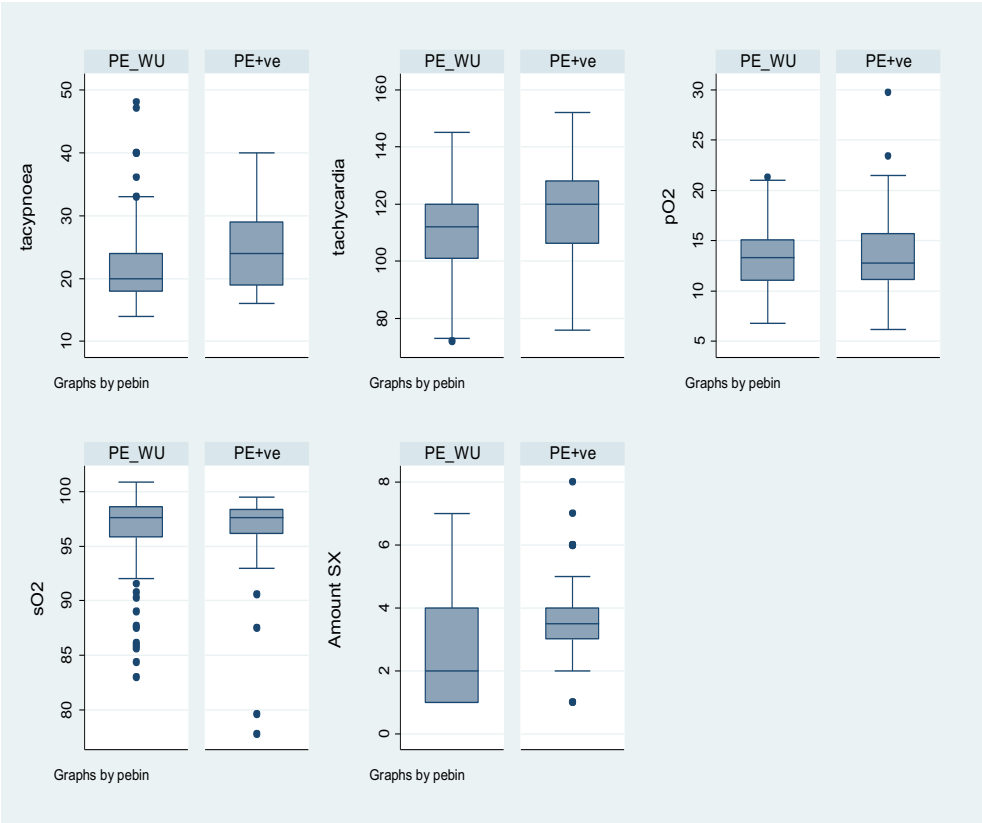

Figure 6: Box and whisker plot of PE signs and symptoms

Chest pain (p=0.01), haemoptysis (p=0.07), tachypnoea (p=0.01) and tachycardia (p=0.03) were all statistically significant clinical features. The highest statistical significance were patients presenting with a cough (p<0.01). There were minimal patients with hypoxia and hypoxemia in both groups with a median of (12.8 vs 13.3; 97.6 vs 97.6), respectively and was not statistically significant.

The individuals with pulmonary embolism had more symptoms and signs than those without pulmonary embolism [3.5(3-4) vs 2(1-4)] with a highly significant p-value of 0.01.

As listed in Table 8 the stepwise logistic regression for univariate analysis selected all the signs and symptoms into the model. The model tested the effect of the symptom or sign on the outcome in patients with a positive pulmonary embolus. Coughing (OR=3.83; 95% CI: 1.71 to 8.58; P<0.01), chest pain (OR=2.57; 95% CI: 1.2 to 5.53; P=0.02), tachycardia (OR=1.03; 95% CI: 1,0 to 1.06; P=0.03), tachypnoea (OR=1.06; 95% CI: 1.0 to 1.12; P=0.05) and a median symptom of 3.5 (1.58; 95% CI: 1.23 to 2.06; P<0.01) were the best explanatory variables.

The stepwise logistic regression for the multivariate analysis selected all the signs and symptoms of the univariate analysis with a P-value<0.1. Leg pain, leg swelling, syncope, dizziness, hypoxia and hypoxemia were poor explanatory variables and were not selected. The model tested if the symptom or sign persisted in the presence of other symptoms and signs. Both tachycardia (OD=1.03; 95% CI: 1.0 to 1.06; P=0.03) and coughing (OD=3.43; 95% CI: 0,88 to 11.0; P=0.05) were positive predictors for pulmonary embolus.

A further logistic regression for tachycardia were conducted. The study determined that the clinical utility of tachycardia is more practical if used in increments of 5 beats per minute. Figure 8 represents the odds ratio of pulmonary embolus using logistic regression of tachycardia with increments of 5 beats per minute. There were a 23% increase in pulmonary embolus for every increase of 5 beats per minute in the heart rate above 100Bpm. This association was statistically significant (p=0.0004)

In addition a logistic regression analysis of the association between tachycardia, tachypnoea and chest pain and the risk of having a pulmonary embolus was conducted. In the combined regression, there were a 4% increase in the risk of pulmonary embolus for every single unit increase in heart rate. When controlling for tachycardia and tachypnoea, chest pain was also associated with a 3.8 times increase in the odds of having a pulmonary embolus. This association were statistically significant (p=0.0001)

Figure 7: Logistic regression of increases in heart rate of 5 beats per minute and risk of having a pulmonary embolus

```
Logistic regression                                     Number of obs   =        184
                                                        LR chi2(1)      =      12.51
                                                        Prob > chi2     =     0.0004
Log likelihood = -86.096203                             Pseudo R2       =     0.0677

------------------------------------------------------------------------------
          pe |      Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    tachy_5  |       1.233533    .07913     3.27   0.001     1.087794    1.398796
       _cons |       .0023761   .0035068    -4.09   0.000     .0001317    .0428667
------------------------------------------------------------------------------
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Figure 8: Logistic regression of risk factors of having a Pulmonary Embolus

Logistic regression — Number of obs = 159
LR chi2(3) = 20.19
Prob > chi2 = 0.0002
Log likelihood = -76.16497 — Pseudo R2 = 0.1170

pe	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
tachycardia	1.040174	.0145955	2.81	0.005	1.011957	1.069178
tacypnoea	1.041473	.0308423	1.37	0.170	.9827439	1.103712
chestpain	3.846443	1.638608	3.16	0.002	1.668946	8.864951
_cons	.0008542	.0014717	-4.10	0.000	.0000292	.0250048

Discussion

VTE impacts patient's lives, not only due to the increased morbidity associated with it, but also the increased risk of mortality. This effect is even more pronounced when VTE occurs in the peri-partum period. There are significant implications on delivery plans, future options of contraception and thromboprophylaxis in the subsequent pregnancies. At present, there is no pre-test probability assessments for predicting VTE in pregnancy. The motivation of this study, was to examine the clinical presentation of patients managed at a tertiary level maternity centre in an attempt to reveal possible predictors and to resolve the diagnostic dilemmas that occurs at times.

Primary Outcome

The absolute incidence of VTE in pregnancy and puerperium at the maternity unit was 1.2 per 1,000 deliveries, which is similar to the incidence from other studies worldwide. It was comparable to the incidence of other third world countries like Saudi Arabia (1.25 per 1,000 deliveries)[21]and China (1.88 per 1,000 deliveries)[20]. It was also similar to first world countries like Australia (1.14 per 1,000 deliveries)[18], UK (1.14 per 1,000 person-years)[10] and the USA (1.72 per 1,000 deliveries).[19]

A previous study investigated the incidence of newly diagnosed VTE's at Groote Schuur Maternity Centre. They found an incidence of 0.55 per 1,000 deliveries.[22] This study only included patients that had been newly diagnosed with a VTE in pregnancy and did not include the post-partum period. We feel the current study is a better presentation of the epidemiology of VTE's in pregnant and postpartum patients in the Metro-west area in Cape Town.

The absolute incidence of DVT was 0.2 per 1,000 deliveries, which is lower than that found in other studies. Previous studies found an incidence of 1.2-1.5 per 1,000 deliveries with a higher ratio of DVT's compared to PE's.[2, 16, 19, 54] In our study, this ratio was inverse. It is possible that our incidence of DVT's could be underestimated, given that a patient could have been diagnosed at other hospitals or emergency centres.

The absolute incidence of PE was 1.1 per 1,000 deliveries. This is comparable to a study done in the USA in NY between 2003-2008 (1.1 per 1,000 deliveries).[55] This incidence is higher than other studies done in the USA (0.48 per 1,000 deliveries and 0.36 per 1,000 deliveries)[8, 19], Canada (0.54 per 1,000 deliveries)[16] and Scotland (0.3 per 1,000 deliveries)[15]. This may be due to patients that present late when a PE has already been formed, due to the low socio-economic background of the population examined, with resultant reduced access to transport and delayed presentation to tertiary care for diagnosis and treatment. Further studies will be

necessary to look at the ratio of DVT's and PE's in South Africa, to see if this is a true presentation of the population.

The total number of VTE's diagnosed in the first trimester was one (3%), nine in the second trimester (23%), 18 in the third trimester (46%) and 11 in the postpartum period (28%). A large proportion of VTE's were diagnosed in the third trimester, consistent with a study done in the USA[19] and a meta-analysis where two thirds of DVT's occurred antepartum and one third postpartum.[56] The MEGA study, a large population-based case-control study also showed the highest risk of VTE occurred in the third trimester of pregnancy and during the first six week after delivery.[9]

Our incidence for VTE postpartum was lower than other studies. This may be due to thromboprophylaxis antenatally and postpartum. At this facility, all patients undergoing caesarean sections or have a high risk vaginal delivery, receives clexane until discharge from the hospital. The design of the study did not include the late postpartum patients who presented after discharge. These patients would be managed in the Gynaecology Department and not the maternity centre. This may also have contributed to a lower incidence.

The majority of PE's were diagnosed with an VQ scan. According to local protocol, VQ scans are the diagnostic study of choice to diagnose a PE. CTPA studies were utilised only if concurrent lung pathology were found or logistic limitations were experienced in obtaining a VQ scan.

The predominance of DVT's occurring in the left leg (66.75%) rather than the right leg (33.3%) is in accordance with previously published studies. This left- sided predominance during pregnancy is thought to be due to a relative stenosis of the left common iliac vein, where it lies between the lumbar vertebral body and the right common iliac artery. Studies also suggest a temporary or reversible May-Thurner syndrome brought on by compression of the left common iliac vein by the enlarged, gravid, uterus where the right iliac artery crosses the vein[6]

Secondary Outcomes

This study showed that among patients with a DVT, the most frequently reported symptoms were leg pain (66.7%), leg swelling (66.7%) and tachycardia (66.7%). They also presented with a higher pulse rate compared to the patients without a DVT. Coughing and haemoptysis was the only symptoms that showed some significance. These symptoms are not typical of DVT and more likely a symptom of PE.

Previous studies have shown that the most common presenting symptoms of DVT in pregnant and postpartum woman were swelling (88% of pregnant woman and 79% of postpartum women) and extremity discomfort (79% of pregnant women and 95% of postpartum

women).[57] These rates are comparable to the rates found in this study. It is important to note that symptoms may be masked by the swelling and discomfort that accompany normal pregnancies.

A number of studies also examined the accuracy of symptoms and signs in diagnosing DVT in the non-pregnant population. These studies showed no proven usefulness between patients with and without a DVT. [58]This study suggests that signs and symptoms must be used in combination with risk factors to determine the clinical suspicion of a DVT and to refer them timeously for diagnostic testing.

There is a large number of patients that present to Groote Schuur Maternity Centre with a tachycardia, in pregnancy or postpartum, without any other signs and symptoms of a VTE. When these patients were worked up for a VTE a large amount of them had a positive VQ scan. The study thought it would be worthwhile to evaluate this phenomenon and to see if it had any significance.

Among patients with pulmonary embolus, the most frequently reported symptoms were tachypnoea (78.4%), dyspnoea (64.9%), tachycardia (62.2%), chest pain (51.4%) and coughing (46%). They presented with a higher heart rate and respiratory rate then patients without a PE. The univariate analysis showed that all the above-mentioned signs and symptoms except dyspnoea, were statistically significant. The median amount of three point five symptoms, in patients with a PE also showed statistical significance.

The multivariate analysis showed that coughing, and tachycardia were good explanatory variables to predict a positive pulmonary embolus, although coughing had a very wide confidence interval. This could be explained on the basis of a small study population.

The logistic regression for tachycardia showed that every increase of five beats per minute above 100Bpm increased the risk of developing a PE with 23%. This association was statistically significant (p=0.0004)

The study also found an association between tachycardia, tachypnoea and chest pain and the risk of having a pulmonary embolus. In the combined regression, there were a 4% increase in the risk of pulmonary embolus for every single unit increase in heart rate. When controlling for tachycardia and tachypnoea, chest pain was also associated with a 3.8 times increase in the odds of having a pulmonary embolus. This association were statistically significant (p=0.0001)

Three previous studies in the USA also looked at the clinical presentation of PE in pregnancy and postpartum. Cahill *et al*[41] found that the most common reason a patient underwent evaluation for PE was shortness of breath (60%), followed by tachycardia (54%) and desaturation less than 95% (40%). There was no significant risk association between specific

clinical symptoms and findings and the risk of pulmonary embolism. The factor with the greatest risk association was a PaO_2 less than 65 mmHg, but it was not sufficiently predictive for the diagnosis of pulmonary embolism.

Deutsch *et al*[59] found that chest pain showed some association with a diagnosis of PE, while other signs and symptoms did not. Bourjeily *et al*[60] found that dyspnoea was the most common presenting symptom, followed by chest pain. The study also found no significant difference in the clinical presentation of patients with or without PE.

In comparison with the above-mentioned studies, this study had a larger number of symptoms and signs that where statistically significant. Tachycardia was the most significant in both the univariate and multivariate analysis. It was also statistically significant in the further logistic regressions. The symptoms of chest pain and dyspnoea were present in the population but were not the most common presenting complaint. Coughing was also statistically significant in our univariate analysis. No correlation was found between hypoxia, dyspnoea and hypoxemia, and the diagnosis of PE. There was a correlation found between tachycardia, tachypnoea an chestpain

The Prospective Investigation of Pulmonary Embolism Diagnosis II was a large, prospective, multicentre trial that examined the clinical characteristics of patients with acute pulmonary embolism. Important to note that these patients were from all gender groups and not pregnant or postpartum.[61]New onset dyspnoea at rest or on exertion was the most frequent symptom (67%) in patients with a pulmonary embolism. Tachypnoea was present in approximately one half of patients with pulmonary embolism and tachycardia was present in approximately one quarter[61]. It is comparable to this study where 64.9% patients experienced dyspnoea. The most frequent symptom with a much higher rate than the PIOPED II study was tachypnoea at 78.4%. Tachycardia (62.2%) was also higher in this study population. It may be as a result of physiological changes of the respiratory, cardiovascular and haematological systems in pregnancy and the puerperium. In this study as well as the PIOPED studies, pleuritic chest pain was more frequent in patients with PE than haemoptysis. Signs of a DVT (oedema, erythema, or tenderness) was rare.

A systemic review performed in patients with suspected and diagnosed PE in the emergency department, showed that an increased heart rate and a reduced pulse oximetry reading increased the probability of PE.[62] Pregnant and post-partum patients were also included in this study. Tachypnoea was a less predictive value although studies were inconsistent. Two studies found that it was significantly associated with PE.[62] In comparison to this study tachycardia and tachypnoea were significant but again there wasa no statistical significance for hypoxemia or hypoxia.

Study Strengths & Limitations

Strengths:

- First study looking at the epidemiology of VTE in the pregnant and post-partum population in South Africa and the African continent
- All the folders were retrieved

Limitations:

- Small retrospective study
- Only woman with a clinical suspicion of VTE were tested for this condition
- Postnatal events would be underreported because the data analysed was only in the early postpartum period until patients were discharged from our maternity centre and not six weeks post delivery
- Pregnancy related VTE may not initially present to our study site especially when in the first trimester. Although all patients with pregnancy related VTE are treated at the maternity unit diagnosis may have occurred elsewhere. This is thought to contribute only to a small underestimation of our results
- The study did not include patients were a VTE was diagnosed at post mortem
- Comparative group in this study was not all pregnant woman, but those with clinical suspicion of VTE that tested negative
- Retrospective nature of this study meant that symptoms and signs were obtained from folder review and there may not have been consistency or standardisation in eliciting symptoms from the doctors who managed the patients in 2016
- General risk factors for VTE were not included in this study

Conclusion

This is the first reported study from South-Africa, to analyse the epidemiology and presenting signs and symptoms, in the local population. The incidence of VTE in this population were the same as in other developed and developing countries around the world. The majority of confirmed VTE's were diagnosed during the third trimester in pregnancy. A lower incidence of DVT's occurred when compared to other studies.

This study also evaluated the clinical factors thought to affect the prediction of VTE in pregnant and postpartum patients. The clinical features that increased probability of PE were chest pain, coughing, tachypnoea, tachycardia and more than three symptoms or signs. Tachycardia were significant in the univariate-, multivariate analysis and further stepwise logistic regressions. There was also a statistically significant association between tachycardia, tachypnoea and chest pain and the risk of having a pulmonary embolus.

This study has revealed the need to develop pre-assessment algorithms in pregnancy and postpartum patients to reduce maternal and fetal, morbidity and mortality. Until such algorithms are developed, clinicians should use their own clinical judgment and proceed to diagnostic imaging for suspected VTE, where indicated.

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Appendices

Table 1: Baseline characteristics of the cohort stratified by Pulmonary Embolism (N=147)

Characteristic	Total (N=186)*	Total (N=147)**	PE + (n=37)	PE – (n=110)
Doppler's, n (%)				
Left	25 (13.4)	3 (2.0)	1 (2.7)	2 (1.8)
Right	25 (13.4)	3 (2.0)	1 (2.7)	2 (1.8)
CTPA, n (%)	31 (16.7)	30 (20.4)	2 (5.4)	28 (25.5)
VQ, n (%)	118 (63.4)	117 (79.6)	34 (91.9)	83 (75.5)
DVT, n (%)				
Yes	6 (3.2)	2 (1.5)	2 (5.4)	0
No	38 (20.4)	3 (2.2)	0	3 (2.7)
Antepartum, n (%)	108 (58.1)	83 (56.5)	27 (73.0)	56 (50.9)
Postpartum, n (%)	78 (42.2)	64 (46.7)	10 (27.0)	54 (49.1)
Trimester, n (%)				
First	3 (1.6)	2 (1.4)	1 (2.7)	1 (0.9)
Second	40 (21.5)	30 (20.4)	8 (21.6)	22 (20.0)
Third	65 (35.0)	51 (34.7)	18 (48.7)	33 (30.0)

* Total number of patients worked up for VTE (Total = 199 studies; 13 patients had more than one study)

** Total of number of patients worked up for PE

Table 2: Baseline characteristics of the cohort stratified by Deep Venous Thrombosis (N=44)

Characteristic	Total (N=186)***	Total (N=44)****	DVT + (n=6)	DVT – (n=38)	p-value
Doppler's, n (%)					
Left	25 (13.4)	25 (56.8)	4 (66.7)	21 (55.3)	0.60
Right	25 (13.4)	25 (56.8)	2 (33.3)	23 (60.5)	0.21
CTPA, n (%)	31 (16.7)	3 (6.8)	1 (16.7)	2 (5.3)	0.30
VQ, n (%)	118 (63.4)	3 (6.8)	0	3 (7.9)	0.48
PE, n (%)					
Yes					
No					
Antepartum, n (%)	108 (58.1)	27 (61.4)	4 (66.7)	23 (60.5)	0.77
Postpartum, n (%)	78 (42.2)	17 (38.6)	2 (33.3)	15 (39.5)	0.77
Trimester, n (%)					
First	3 (1.6)	1 (2.3)	0	1 (2.6)	0.69
Second	40 (21.5)	11 (25.0)	1 (16.7)	10 (26.3)	0.61
Third	65 (35.0)	15 (34.1)	3 (50.0)	12 (31.6)	0.38

*** Total number of patients worked up for VTE (Total = 199 studies; 13 patients had more than one study)

**** Total of number of patients worked up for PE

Table 3: Baseline symptoms of the cohort stratified by DVT (N=44)

Characteristic	Total (N=186)***	Total (N=44)***	DVT + (n=6)	DVT – (n=38)	p-value
Leg pain, n (%)	27 (14.5)	26 (59.1)	4 (66.7)	22 (57.9)	0.69
Leg swelling, n (%)	40 (21.5)	33 (75.0)	4 (66.7)	29 (76.3)	0.61
Dyspnoea, n (%)	82 (44.1)	7 (15.9)	2 (33.3)	5 (13.2)	0.21
Chest pain, n (%)	51 (27.4)	2 (4.6)	0	2 (5.3)	0.57
Haemoptysis, n (%)	5 (2.7)	1 (2.3)	1 (16.7)	0	0.01
Syncope, n (%)	4 (2.2)	1 (2.3)	0	1 (2.6)	0.69
Dizziness, n (%)	9 (4.8)	1 (2.3)	0	1 (2.6)	0.69
Coughing, n (%)	39 (21.0)	4 (9.1)	2 (33.3)	2 (5.3)	0.03
Median number of symptoms and signs	2.5 (1.5 – 4.0)	2 (2 – 3)	3 (3 – 4)	2 (2 – 3)	0.08

*** Total number of patients worked up for VTE (Total = 199 studies; 13 patients had more than one study)

**** Total of number of patients worked up for PE

Table 4: Baseline signs of the cohort stratified by DVT (N=44)

Characteristic	Total (N=186)***	Total (N=44)****	DVT + (n=6)	DVT – (n=38)	p-value
Red discolouration, n (%)	4 (2.2)	4 (9.1)	0	4 (10.5)	0.41
Warmth, n (%)	4 (2.2)	4 (9.1)	1 (16.7)	3 (7.9)	0.49
Cellulites, n (%)	4 (2.2)	4 (9.1)	0	4 (10.5)	0.41
Tachypnoea, median (bpm)	20 (18-25)	20 (18 – 24)	19 (18 – 40)	20 (18 – 24)	0.90
Tachycardia, median (Bpm)	110 (97-120)	95 (83 – 108)	107 (87 – 109)	93.5 (82 – 104)	0.21
pO_2, median (mmHg)	13.2 (11.0-15.3)	13.6 (10.5 – 14.2)	10.3 (8.0 – 12.6)	14.1 (11.8 – 14.8)	0.12
sO_2, median (%)	97.6 (95.8-98.5)	97.5 (95 – 98)	94.1 (90.6 – 97.5)	97.8 (96.9 – 98.0)	0.24
Median number of symptoms	2.5 (1.5 – 4.0)	2 (2 – 3)	3 (3 – 4)	2 (2 – 3)	0.08

*** Total number of patients worked up for VTE (Total = 199 studies; 13 patients had more than one study)

**** Total of number of patients worked up for PE

Table 5: Baseline symptoms of the cohort stratified by Pulmonary Embolism (N=147)

Characteristic	Total (N=186)*	Total (N=147)**	PE + (n=37)	PE – (n=110)	p-value
Leg pain, n (%)	27 (14.5)	2 (1.4)	1 (2.7)	1 (0.9)	0.42
Leg swelling, n (%)	40 (21.5)	9 (6.1)	4 (10.8)	5 (4.6)	0.17
Dyspnoea, n (%)	82 (44.1)	78 (53.1)	24 (64.9)	54 (49.1)	0.10
Chest pain, n (%)	51 (27.4)	51 (34.7)	19 (51.4)	32 (29.1)	0.01
Haemoptysis, n (%)	5 (2.7)	5 (3.4)	3 (8.1)	2 (1.8)	0.07
Syncope, n (%)	4 (2.2)	3 (2.0)	1 (2.7)	2 (1.8)	0.74
Dizziness, n (%)	9 (4.8)	8 (5.4)	3 (8.1)	5 (4.6)	0.41
Coughing, n (%)	39 (21.0)	37 (25.2)	17 (46.0)	20 (18.2)	<0.01
Median number of symptoms	2.5 (1.5 – 4.0)	3.0 (1.0-4.0)	3.5 (3.0-4.0)	2.0 (1.0 – 4.0)	<0.01

* Total number of patients worked up for VTE (Total = 199 studies; 13 patients had more than one study)

** Total of number of patients worked up for PE

Table 6: Baseline signs of the cohort stratified by PE (N=147)

Characteristic	Total (N=186)*	Total (N=147)**	PE + (n=37)	PE – (n=110)	p-value
Red discolouration, n (%)	4 (2.2)	0	0	0	-
Warmth, n (%)	4 (2.2)	0	0	0	-
Cellulites, n (%)	4 (2.2)	0	0	0	-
Tachypnoea, median (bpm)	20 (18-25)	20 (18-26)	24 (19-29)	20 (18-24)	0.01
Tachycardia, median (Bpm)	110 (97-120)	113 (102-120)	120 (106-128)	112 (101-120)	0.03
pO_2, median (mmHg)	13.2 (11.0-15.3)	13.2 (11.0-15.3)	12.8 (11.1-15.7)	13.3 (11.0-15.1)	0.81
sO_2, median (%)	97.6 (95.8-98.5)	97.6 (95.8-98.5)	97.6 (96.1-98.4)	97.6 (95.8-98.6)	0.91
Median number of symptoms	2.5 (1.5 – 4.0)	3.0 (1.0-4.0)	3.5 (3.0-4.0)	2.0 (1.0 – 4.0)	<0.01

* Total number of patients worked up for VTE (Total = 199 studies; 13 patients had more than one study)

** Total of number of patients worked up for PE

Table 7: Univariate and multivariate analysis for PE outcome in patients who are PE positive and those negative on PE work-up

Signs and Symptoms	Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
Leg pain, yes	3.02 (0.18 – 49.66)	0.44		
Leg swelling, yes	2.55 (0.65 – 10.03)	0.18		
Dyspnoea, yes	1.91 (0.89 – 4.14)	0.10	0.73 (0.24 – 2.23)	0.58
Chest pain, yes	2.57 (1.20 – 5.53)	0.02	3.43 (0.99 – 11.86)	0.05
Haemoptysis, yes	4.76 (0.76 – 29.71)	0.10	1.68 (0.18 – 16.10)	0.65
Syncope, yes	1.50 (0.13 – 17.04)	0.74		
Dizziness, yes	1.85 (0.42 – 8.16)	0.42		
Coughing, yes	3.83 (1.71 – 8.58)	<0.01	3.15 (0.88 – 11.30)	0.08
Tachypnoea, (bpm)	1.06 (1.00 – 1.12)	0.05	1.03 (0.96 – 1.11)	0.43
Tachycardia, (Bpm)	1.03 (1.00 – 1.06)	0.03	1.03 (1.00 – 1.06)	0.03
$pO_{2,}$ (mmHg)	1.05 (0.95 – 1.17)	0.34		
$sO_{2,}$ (%)	0.97 (0.89 – 1.07)	0.58		
Median number of symptoms	1.58 (1.23 – 2.06)	<0.01	1.03 (0.60 – 1.76)	0.92

Table 8: Univariate and multivariate analysis for DVT outcome in patients who are DVT positive and those negative on DVT work-up

Characteristic	Univariate analysis OR (95% CI)	p-value	Multivariate analysis OR (95% CI)	p-value
Leg pain, yes	1.45 (0.24 – 8.94)	0.69		
Leg swelling, yes	0.62 (0.10 – 3.97)	0.61		
Warmth, yes	2.33 (0.20 – 27.03)	0.50		
Dyspnoea, yes	3.30 (0.47 – 22.98)	0.23		
Coughing, yes	9.00 (0.98 – 82.50)	0.05	9.00 (0.98 – 82.50)	0.05
Tachypnoea, (bpm)	1.06 (0.91 – 1.24)	0.45		
Tachycardia, (Bpm)	1.05 (0.98 – 1.16)	0.18		
$pO_{2,}$ (mmHg)	0.68 (0.36 – 1.26)	0.22		
$sO_{2,}$ (%)	0.69 (0.39 – 1.22)	0.20		
Median number of symptoms	1.55 (0.79 – 3.05)	0.21		

Appendix A

Folder Review Form

Patient number			
PE W/U		DVT W/U	
Antepartum		Postpartum	

If Antepartum:

1st Trimester	2nd Trimester	3rd Trimester

	Yes	No
1. Leg Pain		
2. Leg swelling		
3. Red discoloration		
4. Increased warmth at leg		
3. Cellulites		
4.Dyspnoea		
5. Tachypnoea		
6. Tachycardia		
7. Pleuritic chest pain		
8. Haemoptysis		
9. Syncope		
10. Dizziness		
11. Coughing		
12. Hypoxia		
13. Hypoxemia		

Appendix B

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 November 2017

HREC REF: 822/2017

Dr L Schoeman
Division of Obstetrics & Gynaecology
H-Floor-OMB

Dear Dr Schoeman

PROJECT TITLE: RETROSPECTIVE REVIEW OF THE INCIDENCE OF VENOUS THROMBOEMBOLISM IN PREGNANCY AND THE PUERPERIUM AND IDENTIFICATION OF PRESENTING COMPLAINTS OF PREGNANCY-RELATED VENOUS THROMBOEMBOLISM AT GROOTE SCHUUR MATERNITY CENTRE, CAPE TOWN BETWEEN 1 JANUARY 2016 AND 31 DECEMBER 2016 (MMeD-candidate-Dr C Montgomery)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr C Montgomery will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature removed to avoid exposure online

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 822/2017