Clinical Presentation, Management and Outcomes of Pulmonary Embolism in Pregnancy at a Tertiary Academic Hospital in South Africa

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Haematology.

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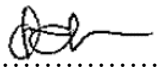
Declaration

I, Nomfundo Candice Andiswa Zulu declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Haematology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



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(Signature of candidate)

On the 29th day of September 2025 in Johannesburg.

Dedication

This thesis is dedicated to my husband, my children and extended family for their unwavering support. Your sacrifices for me to achieve this will never be forgotten.

Presentations and publications arising from the research project

Nomfundo C.A Zulu, Elise Schapkaitz, Jarrod Zamparini, Haroun A. Rhemtula. Pregnancy-Related Pulmonary Embolism: Clinical Characteristics, Management, and Outcomes in a South African Academic Hospital. Submitted to the South African Medical Journal, to be published in January 2026.

Nomfundo C.A Zulu, Elise Schapkaitz, Jarrod Zamparini, Haroun A. Rhemtula. Clinical Presentation, Management and Outcome of Pulmonary Embolism in Pregnancy at Charlotte Maxeke Academic Hospital. Oral presentation at PathRed Pathology Research and Development Congress on the 4th of October 2025.

Abstract

Pulmonary embolism (PE) is a leading cause of death in pregnant and postpartum women. A record review was performed of women with pregnancy-related PE to evaluate their clinical presentation, management, and outcomes. These women were managed by a multidisciplinary team at the Charlotte Maxeke Johannesburg Academic Hospital, South Africa from 2018-2024. Thirty-three women with antepartum PE and 44 with postpartum PE were identified. The majority were of African ethnicity and had a median age of 29 years old (interquartile range, IQR = 9). Antepartum risk factors were present in 85.0% with antepartum PE, while postpartum risk factors were found in 96% with postpartum PE. At presentation, chest pain, shortness of breath and palpitations were more common in women with antepartum PE compared to postpartum PE ($p<0.05$). Pre-test probability scores were assessed in a subgroup with d-dimers. Based on the pregnancy-adapted YEARS and Geneva score, imaging would have been required to rule out PE in 87.2% and 73.5% of cases, respectively. Computed tomography pulmonary angiography was the preferred diagnostic modality in 74.0%. Most (97.4%) were treated as inpatients, with 57% requiring initial management in the intensive care unit and/or high care. The median hospital stay was 14 days (IQR = 8). Low-molecular-weight heparin was the most commonly prescribed anticoagulant, with a median treatment duration of 3 months (IQR = 1). The live birth rate was 84.4%. One maternal death occurred; however, this was due to sepsis and unrelated to VTE. The rates of antepartum/secondary postpartum major bleeding and primary postpartum major bleeding were 6.5% and 3.9% respectively. In conclusion, this study provides important insights into the clinical characteristics, multi-disciplinary management, fetal and maternal outcomes of pregnancy-associated PE.

Acknowledgements

I would like to express my sincere gratitude to my supervisors Professor E Schapkaitz, Dr J Zamparini and Dr H Rhemtula for their valuable input and continuous support.

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Nomenclature

AARMS	Academic Affairs and Research Management System
APLS	Antiphospholipid Syndrome
ART	Antiretroviral Treatment
BMI	Body Mass Index
CD	Caesarean Delivery
CEO	Chief Executive Officer
CMJAH	Charlotte Maxeke Academic Johannesburg Hospital
CRNMB	Clinically relevant non major bleeding
CTPA	Computed Tomography Pulmonary Angiogram
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CI	Confidence interval
CUS	Compression Ultrasound
DiPEP	Diagnosis of PE in Pregnancy
DVT	Deep Venous Thrombosis
DOAC	Direct oral anticoagulant
GCS	Glasgow Coma Scale
HIV	Human Immunodeficiency Virus
HOD	Head of Department
HREC	Human Research Ethics Committee
ICU	Intensive Care Unit
IQR	Interquartile Range
ISTH	International Society of Thrombosis and Haemostasis
IUGR	Intrauterine Growth Restriction
LMWH	Low Molecular Weight Heparin
LIS	Laboratory Information System
NHLS	National Health Laboratory System
NVD	Normal Vaginal Delivery

OPD	Outpatient Department
OPTICA	Optimised Computed Tomography Pulmonary Angiography in Pregnancy
PE	Pulmonary Embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
RIETE	Registro Informatizado de Enfermedad TromboEmbólica
RPM	Respiration Per Minute
RR	Respiratory Rate
SASTH	Southern African Society of Thrombosis and Haemostasis
SAVE	Study on Assessment and VTE Evaluation
SPO2	Saturation of Peripheral Oxygen
UFH	Unfractionated heparin
VKA	Vitamin K antagonists
VTE	Venous Thromboembolism
VQ	Ventilation Perfusion

1 INTRODUCTION AND LITERATURE REVIEW

1.1 Background

Pregnancy induces physiological changes in haemostasis that predispose to venous thromboembolism (VTE). In addition, risk factors that further increase this risk have been described.[1,2] However, local studies are limited.[3] Pulmonary Embolism (PE) is an important preventable cause of maternal morbidity and mortality and it is concerning that VTE related maternal mortality has remained unchanged in the past three triennia in South Africa.[4] This warrants improving the awareness to the health care services of the recommended VTE prevention guidelines. The aim of this study was to review the hospital records of women who developed PE during pregnancy and the postpartum period at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in order to improve the management and outcomes of this high-risk population.

1.2 Literature review

1.2.1 Epidemiology of Pregnancy-related Venous Thromboembolism

VTE includes deep venous thrombosis (DVT) and PE. The incidence of VTE in pregnancy in high income countries is approximately 1-2 per 1000 deliveries. A higher VTE incidence of 3.8-5 per 1000 deliveries has been reported in women of African ethnicity. The incidence of VTE is 4-5 times higher in pregnant women as compared to the non-pregnant population, and this incidence increases to about 5-15 times in the postpartum period.[5,6] Approximately half of pregnancy-related VTE events occur during pregnancy, and the other half in the first six weeks postpartum. Of the VTE cases, 20 to 30 percent present as PE.[7]

Pulmonary embolism accounts for approximately one death in every 100,000 deliveries globally. In the most recent Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRRACE) report of Maternal Mortality in the United Kingdom and Ireland (2020-2022), thrombosis and thromboembolism was the leading direct cause of death.[8] In South Africa, a resource limited country, PE is one of the top ten causes of preventable maternal deaths. The three leading causes identified by the confidential enquiries were

hypertensive disorders, non-pregnancy related infections and obstetric haemorrhage. Nonetheless, what is of concern is that there has not been a significant decrease in the rates of maternal deaths due to PE over the past three triennia.[4] Moreover, over 50% of deaths due to PE were preventable.[4] Since PE is not among the leading causes of maternal mortality in South Africa, this may have led to decreased awareness and research into this cause of death. This is also evident by the scarcity of research done on pregnancy-related PE in South Africa.[3]

1.2.2 Risk Factors for Pregnancy-related Venous Thromboembolism

In pregnancy and the puerperium, physiological and anatomical changes occur as a result of the enlarging uterus, hormonal changes, hypercoagulability and trauma to the endothelium during delivery. These changes all contribute to the increased risk of VTE in this population.[1] In addition, antepartum and postpartum risk factors which further increase this risk have been identified. A personal history of thrombosis and inherited thrombophilia have been shown to be high risk factors for VTE.[2] There are also several clinical risk factors which are associated with an intermediate to low risk of VTE. These include; obesity, age above 35 years, multiparity, medical co-morbidities, significant pregnancy complications and caesarean delivery (CD).[9]

A VTE risk assessment is recommended in early pregnancy as well as the postpartum period. The presence of risk factors and their level of risk provides guidance on the indications for antepartum and postpartum thromboprophylaxis. Several guideline recommendations have been published.[9,10,11] For example, according to the South African recommendations, in pregnant women at intermediate risk, clinical monitoring or low molecular weight heparin (LMWH) thromboprophylaxis during pregnancy and for at least two weeks postpartum is recommended. In women at high risk, thromboprophylaxis during pregnancy and for six weeks postpartum is recommend.[12]

According to a recent systematic review, antepartum and postpartum thromboprophylaxis is underutilized.[3] This study of research that had been published in Africa on VTE up to 2016 showed that 25% of patients at risk of VTE did not receive thromboprophylaxis.[3] A similar result was found in the Study on Assessment and VTE Evaluation (SAVE) study. This was an

international study on VTE risk assessment and management during pregnancy and the puerperium.[13] Analysis of the South African sub-group revealed that 50% of healthcare professionals were unaware of existing VTE guidelines.[14] In the study, approximately 28% of postpartum patients were assessed as high risk for VTE. However, only 50% of them received 6 weeks of post-partum thromboprophylaxis as proposed by the guidelines.

1.2.3 Clinical Presentation and Diagnosis of Pregnancy-related Venous Thromboembolism

The diagnosis of VTE in pregnancy can be challenging. The absence of population-specific, pregnancy-adjusted reference intervals for d-dimer makes it challenging to reliably use the test to rule out VTE during pregnancy.[15] The d-dimer increases during pregnancy and radiological investigations are often required when the diagnosis is clinically suspected. Radiological imaging, however, may expose the mother and baby to harmful ionizing radiation. The preferred investigations in pregnancy are compression ultrasound, CT pulmonary angiography (CTPA) and ventilation-perfusion (VQ) scanning.[16]

Diagnostic algorithms, which consider clinical probability and d-dimer, have been investigated to rule out PE. A multi-centre management outcome study investigated the revised Geneva score with addition of a d-dimer in those of low and intermediate risk pre-test probability. In women with a low or intermediate pre-test probability there were no symptomatic VTE events after three months of follow-up (0.0%, 95% confidence interval [CI], 0–1.0%). A PE was ruled out and imaging avoided in 11.6% of women with a low or intermediate pre-test probability and d-dimer <0.5 µg/ml.[17] Nonetheless, the Geneva score includes variables such as age >65 years, and malignancy, which are not relevant to a pregnant population. In addition, clinical signs such as heart rate have differing thresholds in pregnancy because of the associated hemodynamic changes. More recently, a Geneva score adapted to pregnant women with suspected PE has been proposed.[18] The pregnancy-adapted YEARS algorithm combined three diagnostic criteria with the d-dimer.[19] The diagnostic criteria included clinical signs of DVT, haemoptysis, and PE as the most likely differential. The YEARS algorithm was associated with a reduction in CTPA imaging in 39% of pregnant women with suspected PE. Of interest, a PE was more frequently confirmed in the presence of diagnostic criteria and an elevated d-dimer versus an isolated elevated d-dimer (7% versus 1%). A post hoc analysis of the YEARS algorithm found no VTE on follow-up (0%, 95% CI, 0–3.9).[20] The risk–benefit ratio and cost-

effectiveness of such algorithms could prove particularly useful in a low resource setting. These require prospective validation in the South African pregnant at risk population.

1.2.4 Management of Pregnancy-related Venous Thromboembolism

Heparins, which include LMWH and unfractionated heparin (UFH), can be used safely in pregnancy for the management of PE.[10] In contrast to vitamin K antagonists (VKA) and the direct oral anticoagulants (DOAC), heparins do not cross the placenta. VKA such as warfarin and the DOAC are not recommended for the management of VTE in pregnancy.[10] Systemic thrombolytic therapy can be administered with heparin in acute massive PE associated with life-threatening hemodynamic instability.[10] LMWH is the preferred treatment of VTE in pregnancy.[10,29] LMWH is associated with lower risks of maternal complications such as reduced bone density, osteoporotic fracture and heparin-induced thrombocytopenia as compared to UFH. Additional advantages include; predictable pharmacokinetics, a longer half-life, subcutaneous administration and reduced monitoring requirements.[10,29] The side effects of LMWH include skin hypersensitivity reactions, bruising and bleeding. The risk of bleeding is highest at delivery and a planned management of delivery is recommended in order to reduce the associated risks of maternal postpartum haemorrhage (PPH). According to a recent systematic review, the rates of PPH from 13 studies, including 725 women receiving anticoagulation, were not significantly increased as compared to pregnant women not receiving anticoagulation. Major bleeding occurred in 1.9%, clinically relevant non-major bleeding in 5.7% and minor bleeds in 28.3% of patients.[22]

At delivery, a scheduled delivery is preferable in order to minimize the duration of time without anticoagulation, especially in high risk pregnancies (VTE one month prior to delivery).[10] A time interval of 24 hours is recommended between the last therapeutic LMWH dose and delivery/neuraxial anaesthesia.[10] Likewise a time interval of 12 hours is adequate for prophylactic LMWH.[10] After delivery, it is recommended that LMWH should be reintroduced at least six hours after delivery/removal of the catheter, provided haemostasis is adequate.[10] In the postpartum period, LMWH, fondaparinux and VKA are safe, while the DOAC should be avoided in breastfeeding women. Anticoagulation should be continued until six weeks postpartum for a minimum of three months in total.[11]

1.2.5 Outcomes of Pregnancy-related Venous Thromboembolism

Pulmonary embolism is associated with long term complications, in particular VTE recurrence and chronic thromboembolic pulmonary hypertension (CTEPH). The two year risk of VTE recurrence is estimated to be 3.3% (95% CI 1.5-5.0) for women whose initial event was pregnancy-related.[23] Another long-term complication is CTEPH which is rare following pregnancy-related PE. It is characterised by increased pulmonary vascular resistance and cardiopulmonary complications. A prospective ten-year study that monitored patients with PE reported an incidence of CTEPH of 3.1% (95% CI, 1.1-6.5). The highest cumulative risk of 4.0% occurred two years after PE.[24] In addition, post-thrombotic syndrome is a frequently reported complication of pregnancy-related VTE. Prevention, prompt diagnosis and treatment for an adequate duration are important to prevent these long-term complications.

1.3 Study Aim and Objectives

Pregnancy induces physiological changes in haemostasis that predispose to VTE. In addition, risk factors that further increase this risk have been described. Nonetheless, local studies are limited. PE is an important preventable cause of maternal morbidity and mortality and its prevention should be a priority for health care services in South Africa. Of concern, the maternal mortality statistics have remained unchanged in the past three triennia. The aim of this study is to review the hospital records of women who developed PE during pregnancy and the postpartum period at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in order to improve the management and outcomes of this high-risk population.

The objectives of this study are:

1. To describe the antepartum and postpartum risk factors for pregnancy related PE to guide risk stratification and prevention.
2. To review the diagnostic utility of clinical presenting signs and symptoms of pregnancy related PE and d-dimer testing in conjunction with the pregnancy adapted YEARS and Geneva score diagnostic algorithms.
3. To review the radiological diagnosis and management of pregnancy related PE
4. To evaluate the recurrent thrombosis and bleeding outcomes of the study population and subpopulations diagnosed with pregnancy related PE.

2 METHODOLOGY

2.1 Research Design

This is a retrospective record review.

2.2 Ethics Permission

This study was approved by the University of the Witwatersrand Human Research Ethics Committee (M221187). Permission to conduct the study was granted by the Hospital Management, the Head of the Haematology and the Head of Obstetrics and the Academic Affairs and Research of the National Health Laboratory Service (AARMS, NHLS).

2.3 Study Setting

The study was performed at CMJAH, a tertiary hospital in Johannesburg, South Africa. This is a referral hospital for high risk obstetric women.

2.4 Materials and Methods

Patients who were diagnosed with pregnancy related PE at the CMJAH from January 2018 to September 2024 were identified from the Anticoagulation Clinic statistical records in the Department of Haematology. The diagnosis of PE was confirmed in each patient by reviewing the medical records. The data was collected from the hospital records (inpatient files and outpatient files and electronic records in the Departments of Haematology and Obstetrics). Data was collected at presentation, follow-up and completion of treatment. The data was anonymised and coded once all relevant information was collected.

2.5 Selection Criteria

2.5.1 Inclusion criteria

The study included patients with a confirmed diagnosis of PE in pregnancy and up to six-week postpartum period. The diagnosis of PE was considered in women with clinical findings of PE and confirmed with radiologic findings.

2.5.2 Exclusion criteria

Patients with other identifiable causes of VTE such as confirmed DVT alone, superficial vein thrombosis, cerebral sinus vein thrombosis and valve thrombosis were excluded.

2.6 Data Collection

A data collection sheet (Appendix A) was used to collect the following patient information: Clinical data included demographics (age, height, weight, self-identified ethnicity and parity) and relevant medical and obstetric history. Corresponding data on diagnosis, treatment and laboratory investigations was also collected. Antepartum and postpartum risk factors, which are listed in the local thromboprophylaxis risk assessment (Appendix B), were collected. Patients were classified into low, intermediate and high-risk groups for PE in accordance with these recommendations. A past history of VTE was classified as provoked (if it occurred less than three months after a risk factor), unprovoked or pregnancy/oestrogen related. Data with regards to use of, dosing and duration of antepartum and postpartum LMWH thromboprophylaxis was recorded where available.

Presenting clinical symptoms including; chest pain, haemoptysis, dyspnoea, and palpitations, were recorded. Other clinical features including unilateral leg oedema, tenderness, and erythema were also collected. Clinical signs including blood pressure, heart rate, respiratory rate, temperature, level of consciousness and oxygen saturation, were also assessed.

Risk scores were calculated with the pregnancy adapted Geneva score (Appendix C) pregnancy adapted YEARS algorithm (Appendix D) according to clinical signs and symptoms, relevant medical history and d-dimer levels at presentation with PE. According to the pregnancy adapted YEARS algorithm women were classified according to the presence of clinical criteria and d-dimer levels. According to the revised Geneva score, women were classified as low (0-1 point), intermediate (2-6 points) or high (≥7 points) clinical probability of PE according to clinical criteria. Laboratory information was obtained from the laboratory information system (LIS) of the National Health Laboratory Services (NHLS). The d-dimer was collected at presentation and follow-up as a marker of fibrinolysis. The anti-Xa levels, at presentation and follow-up, were recorded antepartum to monitor the therapeutic range of LMWH (0.5-1.0 IU/mL). The international normalised ratios (INR) were collected postpartum to calculate the

time in therapeutic range (TTR). In addition, troponin, full blood count, renal function, thrombotic screen findings, antiphospholipid screen findings were documented. Only blood sampling for thrombotic screen performed post completion of anticoagulation treatment was analysed.

Radiological imaging (VQ scan and/or CTPA), echocardiogram findings and compression ultrasound for the diagnosis of DVT was collected at presentation from the medical records. All PE were objectively verified and all diagnoses were independently reviewed by the study investigators.

The following management of confirmed PE was collected: hospital setting, length of hospital stay, anticoagulant-dose, monitoring, duration of treatment and side effects. Other treatment modalities, i.e., thrombolysis was also included. Complications including; CTEPH and post thrombotic syndrome were documented. CTEPH was radiologically confirmed after completion of anticoagulation. Post thrombotic syndrome is a clinical diagnosis, however was not seen in this cohort within the study period.

Outcomes following diagnosis and treatment of PE included recurrent thrombosis and bleeding. Bleeding was assessed using the ISTH Scientific and Standardization Subcommittee on Control of Anticoagulation bleeding assessment tool for minor, clinically relevant non-major (CRNMB) and major bleeding events related to the use of anticoagulants during pregnancy and the postpartum period (See Appendix E). All bleeding events were confirmed by an independent adjudication committee. (ES, NZ and HR)

As this was a descriptive study on the study population, there was no control group.

2.7 Data Analysis

A sample of 126 women was estimated, assuming a 2.0% incidence of bleeding or recurrent VTE during pregnancy and the postpartum period and considering a maximum incidence of 15%, at a confidence interval (CI) of 95% (Z=1.96) (Epi Info v7.2.0.1, Atlanta, Georgia, USA) and a desired margin of error of approximately 2.4%. During the specified time period (2018-

2024), 77 eligible women were identified. As such, this study was conducted as an exploratory study.

Statistical analysis was performed using StatSoft, Inc. (2016). Statistica (Version 13.2) [Software]. Tulsa, OK: StatSoft. Normally distributed continuous data was presented as mean ± standard deviation (SD) and variables with non-Gaussian distribution as median [interquartile range (IQR)]. Categorical data was presented as frequencies and percentages. The median time to bleeding was estimated using the Kaplan-Meier method and compared between subpopulations using the log-rank test. Statistical significance was set at a p value of <0.05.

3 RESULTS

Seventy-seven women had an objectively diagnosed PE during the study period, including 33 (42.9%) diagnosed during pregnancy and 44 (57.1%) in the postpartum period (Fig 1.).

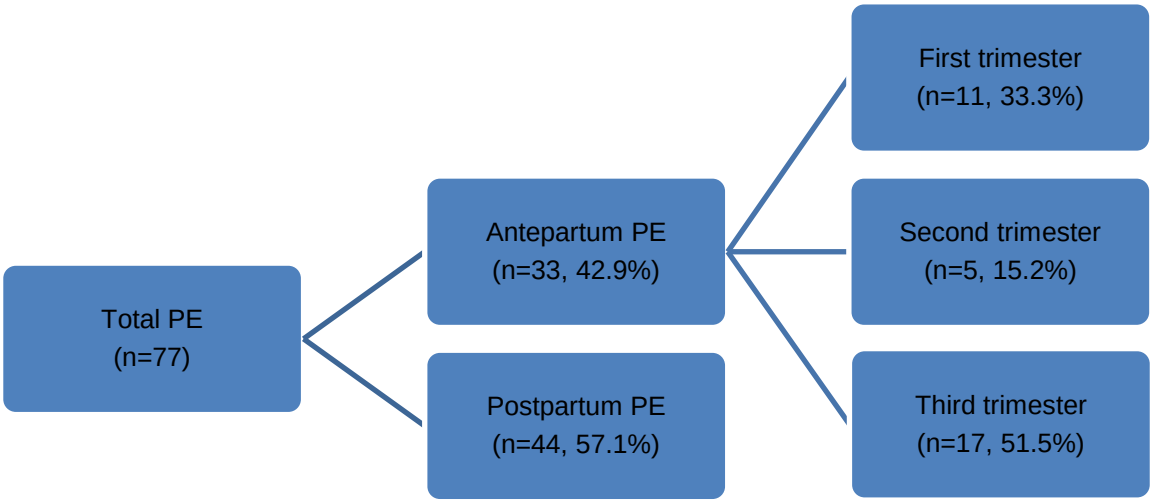


Fig 1. Flow diagram of women in this study

Key: PE, pulmonary embolism

The median [IQR] age was 29.0 [9.0] years and the majority were of Black African ethnicity (n=73, 94.8%). There were 20 women who were living with HIV by delivery. Of these women 15 (19,5%) were diagnosed prior to pregnancy and 5 (6.5%) were diagnosed during pregnancy. The baseline clinical and laboratory characteristics in the women in our cohort are described in Table 1.

Table 1. Baseline characteristics in the pregnant and postpartum women with pulmonary embolism

Characteristics	**Total**	**PE during Pregnancy**	**PE during the Postpartum Period**
Number	77	33	44
Baseline clinical characteristics			
Age at diagnosis (years), median [IQR]	29.0 [9.0]	30.0 [9.0]	29.0 [9.0]
BMI (kg/m^2), median [IQR]	28.6 [12.5]	28.6 [10.9]	28.6 [13.0]
Black African ethnicity (n,%)	73 (94.8)	31 (93.9)	42 (95.5)
Caucasian (n,%)	1 (1.3)	1(3.0)	0 (0)
Coloured (n,%)	1 (1.3)	0 (0)	1 (2.3)
Indian (n,%)	2 (2.6)	1 (3.0)	1 (2.3)
Parity, median [IQR]	2.0 [2.0]	1.0 [2.0]	2.0 [2.0]
Gravidity, median [IQR]	3.0 [2.0]	3.0 [2.0]	2.0 [2.0]
Women with previous miscarriages (n,%)	20 (26.0)	7 (21.2)	13 (29.5)

Smoker (n,%)	1 (1.3)	0 (0)	1 (2.3)
Baseline laboratory characteristics			
Living with HIV (n,%)	20 (26.0)	10 (30.3)	10 (22.7)
CD4 count of those living with HIV (x 10^6/L), median [IQR]	327.5 [372.0]	353.5 [284.0]	296.0 [520.0]
HIV viral load < 50 (copies/ml) of HIV infected, (n,%)	8 (40.0)	4 (40.0)	4 (40.0)
White cell count (x 10^9/L), median [IQR] (ref: 3.9-12.6)	10.4 [4.3]	8.6 [2.8] [2]	11.4 [6.4] [2]
Haemoglobin (g/dL), median [IQR]	10.3 [2.7]	10.7 [2.7]	10.3 [2.8]
Platelet count (x 10^9/L), median [IQR] Pre LMWH Post LMWH	 259.0 [128.0] 307.0 [237.0]	 258.0 [116.0] 235.0 [180.0] [1]	 260.0 [155.0] 345.0 [212.0] [1]
Creatinine (umol/L), median [IQR]	60 [20.0]	57.5 [16.0] [1]	64 [23.0] [1]
GFR (mL/min/1.73 m2), median [IQR]	60.0 [37.0]	81.0 [56.0] [2]	60.0 [0.0] [2]
D-dimer (mg/L), median [IQR] Presentation (n=47) Completion of anticoagulant treatment (n=33)	 3.4 [4.4] 0.2 [0.1]	 3.3 [4.7] 0.2 [0.1]	 3.4 [4.0] 0.2 [0.0]
Troponin T (ng/L), median [IQR]	19.0 [36.0]	16.0 [54.0]	27.5 [21.0]

Key: IQR, inter-quartile range; BMI, body mass index; HIV, human immunodeficiency virus; LMWH, low molecular weight heparin

[1] $p < 0.05$; [2] $p < 0.001$

Additional risk factors in the women in our cohort are listed in Table 2. Of the 59 women with a recorded BMI, 20 (33.9%) had a BMI ≥ 30 kg/m^2. The BMI was calculated based on weight and height at first booking visit at the antenatal clinic. Thrombophilia testing was performed in 44 women (57.1%). Testing revealed a protein S deficiency in 4 (9.1%) and heterozygosity for the non-classical prothrombin gene mutation in 1 (2.3%). The protein S deficiencies were confirmed by low protein S levels after pregnancy and also with repeat testing.

Table 2. Risk factors for pulmonary embolism in the pregnant and postpartum participants

Variable	**n (%)**
Risk factors for PE in pregnancy	**33**
Personal history of VTE	4 (12.1)
Positive family history for VTE	1 (3.0)
Inherited thrombophilia [1]	4 (17.4)
APLS [2]	2 (9.5)
Medical comorbidities [3]	13 (42.4)
Systemic infection	6 (18.2)
Age >35 years	8 (24.2)
Parity ≥3	8 (24.2)
Multiple pregnancy	3 (9.1)
Pre-eclampsia with FGR	3 (9.1)
Hospital admission or immobility	4 (12.1)
Gross varicose veins	1 (3.0)
BMI ≥ 30 kg/m^2 [4]	10 (37.0)
Dehydration/hyperemesis	0 (0)
Risk factors for PE in the postpartum period	**44**
Personal history of VTE	2 (4.5)
Positive family history for VTE	0 (0)

Inherited thrombophilia [1]	1 (4.8)
APLS [2]	2 (9.1)
Medical comorbidities [3]	4 (9.1)
Systemic infection	18 (40.9)
Age >35 years	11 (25.0)
Parity ≥3	12 (27.3)
Multiple pregnancy	6 (13.6)
Pre-eclampsia with FGR	17 (38.6)
Non-obstetric surgery	5 (11.4)
Hospital admission or immobility	16 (36.4)
Gross varicose veins	1 (2.3)
BMI ≥ 40 kg/m^2 [4]	6 (20.0)
Preterm delivery	18 (40.9)
Stillbirth	3 (6.8)
Elective caesarean delivery	31 (70.5)
Emergency caesarean delivery	5 (11.4)
Prolonged labour	2 (4.5)
Post-partum haemorrhage	7 (15.9)

Key: PE, pulmonary embolism; VTE, venous thrombo-embolism; HIV, human immunodeficiency virus; APLS; antiphospholipid syndrome; ART, antiretroviral therapy; FGR, fetal growth restriction; BMI, body mass index

[1] Testing was performed in 23 women with a PE in pregnancy and 21 women with a postpartum PE

[2] Testing was performed in 21 women with a PE in pregnancy and 22 women with a postpartum PE

[3] Medical comorbidities: antepartum included cardiac disease (n=10), active systemic lupus erythematosis (n=1), diabetes mellitus (DM) (n=2), postpartum included: cardiac disease (n=3), DM (n=1), autoimmune hepatitis (n=1)

[4] BMI was recorded in 27 women with a PE in pregnancy and 30 women with a postpartum PE

Of all the women in this cohort, there were 4/33 (12.1%) pregnant and 4/44 (9.1%) postpartum women classified as high risk for VTE, with only 3 of these 8 (37.5%) women receiving thromboprophylaxis in accordance with the SASTH (modified RCOG) guidelines (Table 3). In the high-risk group with antepartum PE, there were four women with a history of VTE, two of

whom also had concomitant protein S deficiency. Among the women with postpartum PE, there were two women with a history of VTE and two with antiphospholipid syndrome (APLS). Additionally, 8/32 (25%) of women classified as intermediate risk in the postpartum period received appropriate thromboprophylaxis, with a similar trend in pregnant intermediate risk women. Among the women with postpartum PE, 31/44 (70.5%) underwent an emergency caesarean delivery, and only 1/44 (2.3%) received postpartum thromboprophylaxis.

Table 3. Risk stratification of study participants according to SASTH (modified RCOG) guidelines

Antepartum	**n (%)**	**Thromboprophylaxis**
High risk	4 (12.1)	0 (0)
Intermediate risk or >4 low risk factors	13 (39.4)	3 (27.3)
Low risk	11 (33.3)	0 (0)
No risk factors	5 (15.2)	0 (0)
Postpartum		
High risk	4 (9.1)	3 (75.0)
Intermediate risk or ≥2 low risk factors	32 (72.7)	8 (25.0)
Low risk	6 (13.6)	2 (33.3)
No risk factors	2 (4.5)	0 (0)

The live birth rate in this study cohort was 65/77 (84.4%). At delivery, 14/24 (58.3%) women with an antepartum PE underwent a scheduled delivery. The median time interval between the last LMWH dose and delivery/neuraxial anaesthesia was 24[15] hours. There was no

significant difference in the time intervals between women with scheduled and unscheduled delivery modes (31 [15] hours vs. 24 [16] hours, p = 0.483). Similarly, the rates of neuraxial anaesthesia did not differ significantly between the two subgroups (p = 0.615).

Table 4. Obstetric and delivery characteristics

Characteristics	**Total**	**Pregnant**	**Postpartum**
Number	77	33	44
Clinical characteristics			
Hypertension (n, %)	32 (41.6)	7 (21.2)	25 (56.8) [1]
Gestational (n, %)	9 (11.7)	2 (6.1)	7 (15.9)
Chronic (n, %)	3 (3.9)	2 (6.1)	1 (2.3)
Pre-eclampsia and FGR (n, %)	20 (26.0)	3 (9.1)	17 (38.6)
Diabetes (n, %)			
Gestational	3 (3.9)	2 (6.1)	1 (2.3)
Delivery characteristics			
Live births (n, %)	65 (84.4)	24 (72.7)	41 (93.2)
Intra-uterine fetal death (n, %)	5 (6.5)	2 (6.1)	3 (6.8)
Miscarriage (n, %)	1 (1.3)	1 (3.0)	0 (0)
Medical termination of pregnancy (n, %)	6 (7.8)	6 (18.2)	0 (0)
Gestational age delivery (weeks), median [IQR]*	37.0 [4.0]	37.5 [2.5]	37.0 [6.0]
Birthweight (g), median [IQR] *	2547.5 [1075.0]	2547.5 [831.5]	2550.0 [1455.0]
Mode of delivery *			
Normal vaginal delivery (n, %)	13 (20)	7 (29.2)	6 (14.6)

Elective caesarean delivery (n, %) Emergency caesarean delivery (n, %)	11 (16.9) 41 (63.1)	5 (20.8) 10 (15.4)	6 (14.6) 31 (75.6)
Anaesthesia (n, %) ** General Epidural/Spinal *Missing data n=13*	 13 (31.7) 28 (68.3)	 6 (46.2) 7 (53.8)	 7 (25.0) 21 (75.0)
Estimated blood loss at delivery (mL), median [IQR] *	500 [300]	500 [400]	600 [225]
Wound sepsis (n. %)	2 (2.6)	0 (0)	2 (4.5)
Postpartum characteristics			
Contraception (n, %) Contraceptive injection Bilateral Tubal Ligation Intrauterine contraceptive –IUD/IUS Condom Oral contraception	41 (53.2) 14 (18.2) 16 (20.8) 1 (1.3) 7 (9.1) 3 (3.9)	14 (42.4) 5 (15.2) 8 (24.2) 1 (3.0) 0 (0) 0 (0)	27 (61.4) [1] 9 (20.4) 8 (18.2) 0 (0) 7 (15.9) 3 (6.8)

Key: IQR, inter-quartile range; FGR, fetal growth restriction

*of live births

**of caesarean deliveries

[1] $p < 0.01$

The baseline PE characteristics and testing performed is presented in Table 5. Pregnant women were more likely to present with symptoms including chest pain, shortness of breath and

palpitations as compared to postpartum women. There were 50 (64.9%) women with a tachycardia of >110 bpm. Signs of DVT were present in 10 (13.0%) women. Compression ultrasound was performed in 14 (18.1%) at diagnosis and the presence of a DVT was verified in 6 (7.8%) of the 77 women. The diagnosis was radiologically confirmed using CTPA in 57 (74.0%) women and V:Q scan in 27(35.1%) women, with 9 women undergoing both investigations. Reasons for both investigations included inconclusive findings on initial investigation (n=7) or negative findings on initial investigation in women with strong clinical suspicion of a PE (n=2). On CTPA, a segmental PE was the most common type of PE (42, 54.5%). A diagnosis of multiple PE was confirmed in 35 (45.5%) women of whom 13 (39.4%) were pregnant and 22 (50.0%) were postpartum.

According to the revised Geneva score, 37 (54.4%) of the pregnant and postpartum women were classified as intermediate risk. D-dimers were performed in 23/37 (62.2%) of the intermediate risk women and were >0.5 mg/L in 20 (87.0%). Similarly, d-dimers were >0.5 mg/L in 9 (90.0%) of the low-risk women. There was no significant difference in the median scores of pregnant and postpartum women (5 [2.5] and 5 [0.5] respectively, p=0.857).

For the application of the YEARS algorithm, d-dimers were not performed in 30 (39.0%) participants. Among the 47 women, according to the algorithm, imaging was indicated to rule out PE in 41 (87.2%). The most common clinical criteria, which was present in 43 (91.5%) women was ‘PE as the most likely diagnosis’. No significant difference between pregnant and postpartum women was observed (p=0.907).

Table 5. Baseline clinical characteristics at PE diagnosis

Clinical Characteristics	**Total**	**Pregnant**	**Postpartum**
Number	**77**	**33**	**44**
Gestational age at diagnosis (weeks), median [IQR]	28.0 [22.0]	28.0 [22.0]	-
Number of days postpartum, median [IQR]	3.0 [6.0]	-	3.0 [6.0]

Symptoms (n, %)			
Chest pain	21 (27.3)	14 (42.4) [1]	7 (15.9)
Shortness of breath	44 (57.1)	24 (72.7) [2]	20 (45.5)
Palpitations	5 (6.5)	5 (15.2) [2]	0 (0.0)
Haemoptysis	2 (2.6)	1 (3.0)	1 (2.3)
Symptoms of DVT	7 (9.1)	5 (15.1)	2 (4.5)
Signs			
Heart rate (bpm), median [IQR]	120 [17]	120 [20]	120 [16]
SBP (mmHg), median [IQR]	126 [25]	126 [21]	126 [25]
DBP (mmHg), median [IQR]	83 [19]	83 [20]	84 [19]
SPO2 (%), median [IQR]	95 [5]	94 [4]	96 [7]
RR (rpm), median [IQR]	20 [10]	20 [8]	22 [6]
Temp (°C), median [IQR]	36.5 [0.3]	36.5 [0.2]	36.5 [0.6]
GCS, median [IQR]	15 [0]	15 [0]	15 [0]
Signs of DVT (n, %)	10 (13.0)	7 (21.2)	3 (6.8)
Scoring			
Revised Geneva score,(n, %)			
low (0-1 points),	10 (14.7)	6 (21.4)	4 (10.0)
intermediate (2-6 points)	37 (54.4)	11 (39.3)	26 (65.0)
high clinical (≥7 points)	21 (30.9)	11 (39.3)	10 (25.0)
insufficient data to complete in scoring n= 9			
Years algorithm (n, %)			
No clinical criteria and d-dimer <1.0 mg/L	0 (0)	0 (0)	0 (0)

No clinical criteria and d-dimer ≥1.0 mg/L	4 (8.2)	1 (4.5)	3 (11.1)
1-3 clinical criteria and d-dimer <0.5 mg/L	6 (12.2)	3 (13.6)	3 (11.1)
1-3 clinical criteria and d-dimer ≥0.5 mg/L	39 (79.6)	18 (81.8)	21 (77.8)
insufficient data to complete in scoring n=28			
Diagnostic investigations (n, %)			
Chest X-ray	52 (67.5)	22 (66.7)	30 (68.2)
Electrocardiogram	68 (88.3)	32 (97.0)	36 (81.8)
Echocardiogram	44 (57.1)	27 (81.8)	17 (38.6)
CTPA	57 (74.0)	24 (72.7)	33 (75.0)
V:Q	29 (37.7)	16 (48.5)	13 (29.5)
Compression ultrasound	14 (18.2)	12 (36.4)	2 (4.5)
D-dimer	48 (62.3)	21 (63.6)	27 (61.4)
Baseline CTPA (n, %) *			
Pulmonary trunk PE	5 (8.8)	3 (12.5)	2 (6.1)
Main pulmonary artery PE	4 (7.0)	2 (8.3)	2 (6.1)
Lobar pulmonary artery PE	11 (19.3)	4 (16.7)	7 (21.2)
Segmental pulmonary artery PE	42 (73.7)	15 (62.5)	27 (81.8)
Subsegmental PE	13 (22.8)	6 (25.0)	7 (21.2)
Pulmonary trunk size, ≥ 30mm	18 (23.4)	10 (30.3)	8 (18.2)
Baseline Echocardiogram**			
Tricuspid annular plane systolic excursion (mm), median [IQR]	23 [9]	21 [10]	23 [5]
Pulmonary artery pressure (mm), median [IQR]	52 [70]	52 [72]	51 [59]
Right ventricular systolic dysfunction (n, %)	10 (22.7)	9 (33.3)	1 (5.9)

Key: DVT, deep vein thrombosis, bpm, beats per minute, SBP, systolic blood pressure, DBP, diastolic blood pressure, SPO2, oxygen saturation, RR, respiratory rate, rpm, respiration per minute, temp, temperature, GCS, Glasgow coma scale, IQR, interquartile range, PE, pulmonary embolism, CTPA, computed tomography pulmonary angiogram, V:Q, ventilation-perfusion scan.

* in 57 participants with a CTPA

**in 44 participants with Echo

[1] $p < 0.01$, [2] $p < 0.05$

The anticoagulant characteristics are presented in Table 6. The majority of women with PE (n = 75, 97.4%) were managed as inpatients. For initial management, 35 (45.5%) were admitted to high care, and 9 (11.7%) to ICU, with no significant difference between women with antepartum PE and postpartum PE. Admission to high care units and ICU was mostly related to haemodynamic instability and co-morbidities. The rest of the women were initially admitted and managed in the general ward. The median length of hospital admission, including the general ward, ICU and high care was 14 days [IQR= 8], with no difference between women with antepartum PE and postpartum PE (p=0.387). In the antepartum period, all pregnant women were treated with LMWH. In the postpartum period, 76 women, initially received LMWH for a median duration of 11 days [IQR= 6]. Thereafter, 35 (79.5%) women and 9 (20.5%) women were treated with warfarin and rivaroxaban respectively.

There was one maternal death in a 38-year-old, who presented with PE at 26 weeks' gestation. A hysterotomy was performed at 29 weeks due to intrauterine fetal death, complicated by uterine necrosis, necessitating a total abdominal hysterectomy. During her admission, she developed sepsis with organ failure and demised of sepsis-related complications.

PE related complications occurred in two women who were diagnosed with CTEPH. The diagnosis was made in consultation with the cardiologist and pulmonologist, who were in agreement with the diagnosis of CTEPH. The first one had an antepartum PE and was diagnosed with CTEPH via VQ scan, 5 months after anticoagulation was initiated. The second woman also had an antepartum PE and was diagnosed with CTEPH via a trans-oesophageal echocardiogram, which was performed 6-7 months after anticoagulation was initiated. There

was also a third woman who was suspected to have CTEPH, however, she was still being monitored at the time of end of the study period.

Table 6. Anticoagulation characteristics

Characteristics			
Number of pregnancies	77	33	44
Management			
Hospital setting (initial management) (n,%)			
OPD	2 (2.6)	2 (6.1)	0 (0.0)
High care inpatient	35 (45.5)	14 (42.4)	21 (47.7)
ICU inpatient	9 (11.7)	5 (15.2)	4 (9.1)
Length of stay, median [IQR]			
High care inpatient	4 [4]	5 [7]	4 [3]
ICU inpatient	7 [2]	7 [1]	7 [6]
General ward inpatient	11 [10]	10 [9]	13 [10]
Anticoagulant			
Medical thrombolysis (n, %)	3 (3.9)	2 (6.1)	1 (2.3)
Catheter-directed (n, %)	1 (1.3)	1 (3.0)	0 (0)
LMWH (n, %)	76 (98.7)	33 (100)	43 (97.7)
Dose (mg bd subcutaneously), mean ± SD	80 [20]	80 [20]	80 [20]
Weight adjusted, (n, %)	49 (64.5)	17 (51.5)	32 (74.4)

Anti-Xa adjusted, (n, %)	27 (35.5)	16 (48.5)	11 (25.6)
Anti-Xa antepartum (IU/mL), mean ± SD	-	0.6 ± 0.3	-
Warfarin postpartum (n, %)	-	-	35 (79.5)
Warfarin daily dose at discharge (mg), median [IQR]	5 [2.5]	5 [1.9]	5 [2.5]
TTR, median [IQR]	-	-	45.3 [55.1]
Rivaroxaban postpartum (n, %)	-	-	9 (20.5)
Duration of treatment (months), median [IQR]	3 [1]	3 [1]	3 [2]
Complications (n, %)			
Skin reactions/ bruising	2 (2.6)	2 (6.1)	0 (0)
Treatment changes due to drug hypersensitivity*	2 (2.6)	2 (6.1)	0 (0)
CTEPH**	2 (5.6)	2 (10.5)	0 (0)
Post thrombotic syndrome ***	0 (0)	0 (0)	0 (0)
Outcomes			
Bleeding, (n, %)			
Minor	3 (21.4)	3 (27.3)	0 (0)
CRNMB	3 (21.4)	2 (18.2)	1 (33.3)
Major	8 (57.1)	6 (54.5)	2 (66.7)
Recurrent VTE, (n, %)	0 (0)	0 (0)	0 (0)
Death, (n, %)	1 (1.3)	1 (3.0)	0 (0)

Key: SD, standard deviation, IQR, inter-quartile range, OPD, outpatient department, ICU, intensive care unit, TTR, time in therapeutic range, CTEPH, chronic thromboembolic pulmonary hypertension, CRNMB, clinically relevant non-major bleeding, VTE, venous thromboembolism.

* The platelet count dropped >50% after 5 days. LMWH switched to Fondaparinux (30 weeks' gestation).

The platelet count dropped >50% after 5 days. UFH switched to LMWH.

**Assessed in 36 participants, 19 with antepartum PE and 17 with postpartum PE.

*** Assessed in 6 participants with DVT

Table 7. Maternal bleeding events

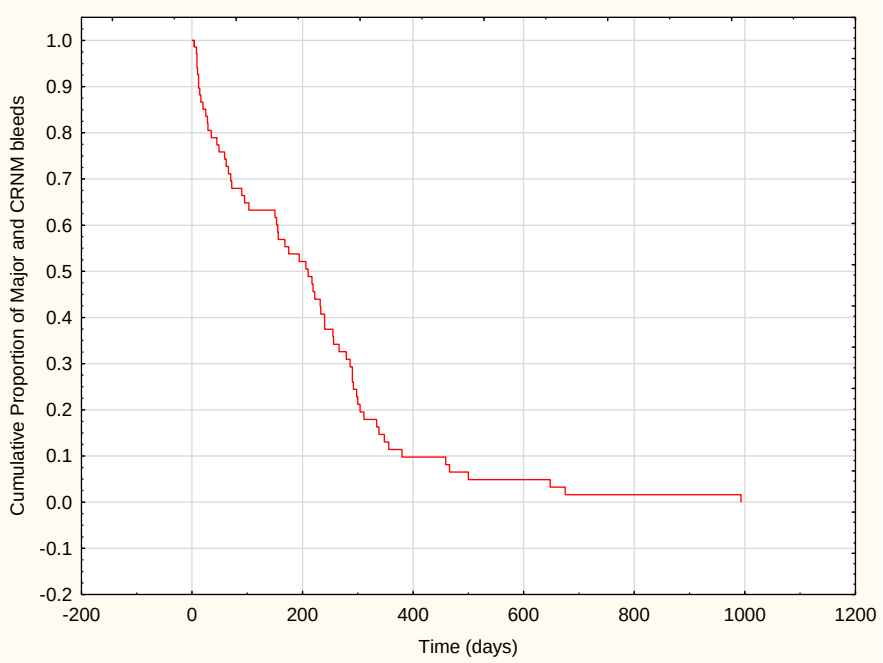
	Description
Antepartum/secondary postpartum	
Major Bleeding	Antepartum PE at 32 weeks' gestation. Day 9 post CD, intra-uterine bleeding occurred on warfarin (INR of 4.13) requiring a relook laparotomy.
	Postpartum PE at day 1. Day 5 post CD, PV bleeding occurred on therapeutic LMWH and required transfusion of 2 units of packed cells.
	Antepartum PE at 32 weeks' gestation. Day 4 post CD, intra-uterine bleeding occurred on therapeutic LMWH requiring a relook laparotomy and packed cell transfusion.
	Postpartum PE at day 3. Day 14 post CD, bleeding from scar occurred on therapeutic LMWH and required transfusion of packed cells and haematoma evacuation
	Antepartum PE at 34 weeks' gestation.

	Day 1 presented with haemoptysis on therapeutic LMWH which required transfusion with 2 units of packed cells.
Clinically relevant non major bleeding	Postpartum PE at day 1. Day 5 presented with haemoptysis on therapeutic LMWH.
	Antepartum PE at 22 weeks' gestation. PV bleeding at 34 weeks' gestation on therapeutic LMWH.
	Antepartum PE at 28 weeks' gestation. Day 5 presented with haematuria on UFH following intra-arterial catheter directed thrombolysis.
Minor bleeding	Antepartum PE at 37 weeks' gestation. PV bleeding occurred at 38 weeks' gestation on therapeutic LMWH.
	Antepartum PE at 36 weeks' gestation. Day 15 post CD with PV bleeding on therapeutic LMWH.
Primary postpartum	
Major Bleeding	Antepartum PE diagnosed at 29 weeks' gestation. Intra-operative bleeding during CD occurred, requiring transfusion with 1 unit of packed cells. LMWH interval was 24 hours from the last dose to delivery.
	Antepartum PE diagnosed at 15 weeks' gestation. Intra-operative bleeding during CD occurred, requiring transfusion with 2 units of packed cells. LMWH interval was not available.
	Antepartum PE diagnosed at 38 weeks' gestation. Intra-operative bleeding during CD occurred, requiring transfusion with 4 units of packed cells. LMWH interval was 24 hours from the last dose to delivery.

Minor bleeding	Antepartum PE diagnosed at 10 weeks' gestation. Delivered at 39 weeks gestation via NVD. PV bleeding occurred within 24hours post NVD. LMWH interval was 16 hours from the last dose to re-initiation of LMWH.
Key: PV, per vagina, LMWH, low molecular weight heparin, NVD, normal vaginal delivery, CD, Caesarean delivery, PE, pulmonary embolism, IUGR, intra-uterine growth restriction,	

The incidence of antepartum/secondary postpartum bleeding was 13.0% (95% CI 7.0-22.5) of which 6.5% (95% CI 2.5-14.7) were classified as major bleeds (Table 7 and Fig 2). The incidence of primary postpartum bleeding was 5.2% (95% CI 1.6-13.0) of which 3.9% (95% CI 0.9-11.3) were major bleeds.

Fig 2. Kaplan–Meier curves of major and clinically relevant non major bleeds in the overall study period



4 DISCUSSION

4.1 Epidemiology of Pregnancy-related Venous Thromboembolism

More than half of pregnancy-related PE events in this low-middle income setting occurred during the first six weeks postpartum. This pattern is consistent with real-world data from the RIETE (Registro Informatizado de Enfermedad TromboEmbólica) registry which showed a peak in VTE incidence in the postpartum period.[7] According to the registry, the incidence of PE in pregnant women was 42% (n = 158) as compared with postpartum women (n = 222, 58%).[7]

4.2 Risk Factors for Pregnancy-related Venous Thromboembolism

Risk factors for VTE were prevalent in this study population, with 85% of women having at least one antepartum risk factor and 96% having at least one postpartum risk factor. Similarly, a study of 21,019 Irish women found that at least one postpartum risk factor for VTE was present in 75% of participants, with approximately 40% having two or more risk factors.[26] Nonetheless, only a few studies have examined risk factors for VTE in women of African ethnicity. Among African women, the risk of VTE has been linked to risk factors, including cardiac disease, HIV infection, chronic hypertension, obesity, sickle cell disease, and inherited thrombophilias such as protein S deficiency and antithrombin deficiency.[1]

The most common antepartum risk factors included medical comorbidities and obesity. It is important to note that 23.3% of the women presented with cardiac disease as a risk factor for antepartum VTE, compared to 0.2% reported in the RIETE registry.[7] In particular, peripartum and hypertension-related cardiomyopathy are key contributors to thrombotic complications in the peripartum period among African women.[26] Maternal obesity is another important risk factor for VTE owing to an increasing prevalence in Africa. According to the international SAVE study on VTE risk assessment, the prevalence of obesity in Africa was 37.7%, with the highest rates observed in South Africa at 44.5%.[13] This trend reflects the broader epidemiological shift in developing regions, where non-communicable diseases are becoming more prominent. Reflecting this pattern, 37% women with an antepartum PE had a BMI $\geq$ 30 kg/m^2 at first booking. Obesity poses an additional challenge in managing thrombosis, as the altered pharmacokinetics necessitate dose adjustments and anti-Xa monitoring of LMWH to

ensure efficacy. Additionally, HIV infection is increasingly recognized as a prothrombotic condition. In this study, 30.3% of the women with antepartum PE were living with HIV, which is consistent with national antenatal rates of 27.5%. Inherited thrombophilias were uncommon in this study population, with a prevalence of 17.4% among those with antepartum PE, compared to 55% in the RIETE registry.[7] The RIETE cohort, primarily recruited from Spain, Italy, France, and Israel, reported a high prevalence of prothrombin gene and Factor V Leiden mutations, which have not been associated with thrombosis among populations of African ethnicity. Postpartum risk factors in this study included elective CD, preterm delivery and systemic infection. To date, clinical risk factors have been associated with a modest effect on VTE risk.[9] The study highlights the need for a large population-based case-control study to determine the significance of clinical risk factors for antepartum and postpartum VTE.

The presence of risk factors as well as their level of risk provides guidance on the indications for antepartum and postpartum thromboprophylaxis. Despite the high prevalence of antepartum and postpartum risk factors in this study population, the underutilization of thromboprophylaxis remains a significant concern. This finding contrasts with the SA SAVE study, which evaluated local practices in VTE risk stratification among pregnant women by experts. In the SA SAVE study, 23 of 126 women (18.3%) were classified as high risk for VTE, 59 (46.8%) as moderate risk, and 44 (34.9%) as low risk.[14] Among those identified as at risk, the majority (82.5%) received thromboprophylaxis. This discrepancy highlights gaps in knowledge and awareness of VTE risk factors, particularly among non-experts, emphasizing the need for improved education to optimize VTE prevention and improve patient outcomes.

In the current study, 75% of high-risk postpartum women received appropriate thromboprophylaxis, however, none of the high-risk pregnant women were administered thromboprophylaxis. Furthermore, postpartum thromboprophylaxis was not routinely prescribed to women who underwent emergency CD, despite the recommendation for at least 7-10 days of thromboprophylaxis in this group. This recommendation is classified as Class IIb, Level C, indicating that it is based on limited evidence or expert opinion, underscoring the need for further robust studies to strengthen the evidence base. Additionally, a limitation of this study is the absence of an assessment of bleeding risks, which could have influenced decisions regarding thromboprophylaxis use and its appropriateness in this high-risk population.

4.3 Clinical Presentation and Diagnosis of Pregnancy-related Venous Thromboembolism

The diagnosis of VTE in pregnancy can be challenging. The clinical presenting signs and symptoms in the study population which most commonly included tachycardia and dyspnoea overlap with the physiological changes of pregnancy. Moreover, only a small proportion had an oxygen saturation <90% on presentation.

An unusual finding in this study was that only 13% of patients presented with signs and symptoms of DVT. This contrasts with the expected concomitant DVT rates of 27% in antepartum and 42% in postpartum women with PE, as reported in the RIETE registry.[7] One possible explanation for this discrepancy is that compression ultrasound (CUS) was not frequently performed, with utilization in 18.1% of the study population. The PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis) study recommended CUS in the setting of a positive d-dimer to limit imaging tests involving ionizing radiation.[28] In the Geneva and YEARS studies, CUS diagnosed DVT in 1.8% and 1.3% of asymptomatic patients respectively, compared to 8.8% and 7% of symptomatic patients.[18,19,20]

CTPA and VQ are recommended for PE diagnosis in pregnancy. Both these diagnostic modalities have negative risk factors associated with radiation exposure to the fetus and breast tissue of the mother, however, the benefits outweigh the risks.[16,29,31] The preferred investigation for the diagnosis of PE in this study was CTPA. CTPA is widely available in most hospitals and is the first-line investigation in many centers in pregnancy, however, the radiation dose protocols vary widely. More recently, the findings of the OPTICA (Optimised Computed Tomography Pulmonary Angiography in Pregnancy) study have been published. This prospective observational study illustrated that a low-dose CTPA protocol in pregnant women suspected of having a PE is safe and effective.[3] CTPA, however, has limitations, as it is influenced by physiological changes in pregnancy. The increased cardiac output needs to be addressed to achieve a high-quality CTPA image. Nonetheless, there is a paucity of large, well-powered studies comparing CTPA and VQ to guide the optimal choice of diagnostic testing for PE in pregnancy.

Studies have investigated the use of d-dimer measurement in combination with clinical decision rules to predict PE in pregnant and postpartum women. The DiPEP (Diagnosis of PE in Pregnancy) study which retrospectively evaluated pregnant or postpartum women with

suspected PE, found no significant predictive value for d-dimer measurement and/or clinical decision rules.[15] However, two recent prospective studies have evaluated this approach in pregnant women: the ARTEMIS study, which applied the pregnancy-adapted YEARS model, and the CT-PE pregnancy study, which used the Geneva Score to safely rule out PE. In this study, the pregnancy-adapted YEARS algorithm, which combines three clinical criteria with d-dimer measurement, was assessed in 47 women.[19] A significant proportion (91.5%) presented with the clinical criterion of 'PE as the most likely diagnosis,' and among them, 86% also had a positive d-dimer. Fewer than 10% of the study population had an isolated positive d-dimer in the absence of clinical criteria. On further investigation of the participants with negative d-dimer measurements a small proportion had commenced anticoagulation (n=2)

The Geneva score adapted for pregnant women did not effectively identify women with a high clinical probability for PE among 68 participants. This contrasts with the CT-PE-Pregnancy study, where the Revised Geneva score successfully categorized pregnant women based on probability of PE, namely; 4% (7/192) in the low-probability group, 9% (18/200) in the intermediate-probability group, and 100% (3/3) in the high-probability group. In the current study, only 21 women (30.9%) were classified as high clinical probability for PE. Tachycardia was the most common presenting symptom, occurring in 51 women. However, the incidence of other criteria was low: surgery (n=15), signs and symptoms of DVT (n=10), personal history of thrombosis (n=6), age >40 years (n=5), and haemoptysis (n=2). Nonetheless, when the Geneva score was combined with a d-dimer test, 87.9% of women classified as low or intermediate risk would have undergone radiological investigation. The cost-effectiveness, of using a d-dimer test in conjunction with the Geneva score could be especially beneficial in low-resource settings.[33] The guidance from the European Society of Cardiology (ESC) has been updated to recommend (class IIa recommendation) a d-dimer and pre-test probability to safely rule out PE during pregnancy or the postpartum period.[31] However, prospective validation in the South African pregnant population at risk is required.

4.4 Management of Pregnancy-related Venous Thromboembolism

In this study, 3.9% of the participants received systemic thrombolysis and 1.3% received a catheter directed thrombolysis. All antepartum PE and 97.7% of postpartum PE received

LMWH, in accordance with guideline recommendations. During pregnancy, the pharmacodynamics of LMWH are altered as a result of the increased volume of distribution and enhanced renal clearance. Routine anti-Xa monitoring to ensure adequate therapeutic LMWH dosing is not recommended. However, some guidelines suggest use of anti-Xa monitoring in those with extremes of body weight and renal impairment.[21,29,31] In pregnancy, the majority of participants received a weight-adjusted LMWH dose (64.5%). Owing to the low number of recurrent VTE or bleeding events, anti-Xa monitoring could not be assessed in this study and future studies are warranted to determine the safety and efficacy of anti-Xa adjusted LMWH. At delivery, 58% of women with an antepartum PE underwent a scheduled delivery. However, an unscheduled delivery was not significantly associated with differences in the duration of time without anticoagulation or access to neuraxial anaesthesia. Postpartum treatment primarily included initial LMWH, followed by warfarin. As the safety of DOACs have not been established in women who are breastfeeding, rivaroxaban was seldom prescribed. There were no cases of IVC filter use, even in the third trimester. The median duration of treatment was 3 months (IQR=1), as recommended by guidelines.[11]

The majority of women were treated as inpatients with 57% requiring initial management in ICU and/or high care. The median length of hospital stay was 14 days (IQR=8 days).

4.5 Outcomes of Pregnancy-related Venous Thromboembolism

The mortality related to PE in this study was zero. There was one maternal death in a woman with a postpartum PE with multiple comorbidities who died during the study period of sepsis-related complications. Bleeding remains a significant safety concern for women receiving anticoagulation. The incidence of antepartum/secondary postpartum major bleeding was 6.5%, consistent with similar studies. Primary postpartum major bleeding occurred in 3.9% of cases. The lower rate may in part be attributed to the discontinuation of enoxaparin at a median of 24 hours (IQR=15) before delivery.

Notably, the rates of both elective and emergency CD were high at this referral centre for high-risk pregnancies, at 17.6% and 60.3%, respectively. A scheduled vaginal delivery remains the preferred mode of delivery in most situations.

4.6 Study limitations

Several limitations of this study warrant consideration. First, this was a single-centre study conducted at a referral centre for patients at risk for obstetric complications. Thus, the study participants represent a selective group of high-risk women in the region. Secondly, the BMI was determined by the weight and height measured at the first ANC visit, this varied amongst the women from this study, ranging from early pregnancy to third trimester. Obesity as a risk factor is best identified with the pre-pregnancy BMI, but this is not practical in this hospital setting. Third, d-dimer levels were conducted in only about half of the participants at presentation which limited interpretation of the pre-test probability scores. Fourth, the study was not designed to assess for long term complications, in particular VTE recurrence, post-thrombotic syndrome and CTEPH. CTEPH was diagnosed in 5.6% of women in this study. Of concern, this rate is higher than reported by a prospective study in patients diagnosed with PE reported a 3.1% (95% CI, 1.1-6.5) incidence of CTEPH over a 10 year period following PE diagnosis.[24] This warrants further investigation. This study was conducted retrospectively, and missing or incomplete data interfered with complete evaluation of each woman in this study. Finally, the lack of a control group precluded a comparative analysis which could have provided additional insights into maternal and fetal outcomes.

5 CONCLUSION

In summary, this study provides important insights into the clinical characteristics, management and outcomes of pregnancy-associated PE in a South African tertiary centre. Risk factors for PE were found in the majority, which can provide guidance for the rational use of antepartum and postpartum thromboprophylaxis. The use of a d-dimer in conjunction with pre-test probability scores offers a potentially cost-effective approach for low resource settings. Future prospective studies are needed to validate these strategies and to better characterize long-term outcomes in the South African pregnant population.

Co-morbidities were increased in this cohort, particularly cardiac disease, which was at a higher rate than reported in global studies. Obesity was another common risk factor in this group, which may be overlooked as a high risk at different levels of care. Local antenatal care clinics would need to be educated on identifying these high risk factors, and referring them to

a higher level of care. This may present an opportunity to consider thromboprophylaxis as suggested by the SASTH obstetric thromboprophylaxis risk assessment guidelines.

Missed opportunities of administration of thromboprophylaxis in this study were mostly noted in high-risk pregnant women and also in women post-delivery via C-section. This further raises the need for education and multidisciplinary involvement of vigilance in identifying high risk patients for VTE.

Maintaining a high clinical suspicion for PE in women who develop unexplained tachycardia is important, as it was the most common presenting sign observed.

D-dimer testing and clinical prediction rules, particularly the YEARS algorithm, demonstrated possible benefit in assessing pregnant and postpartum women with PE in this study population. However, this requires prospective validation in the South African population. The pregnancy adapted Geneva score which does not require d-dimers failed to identify the high-risk group. This suggests that d-dimers, although non-specific, still has an important role in the diagnosis of PE in pregnancy in combination with clinical suspicion.

In this centre, CTPA was the first-line investigation for PE in pregnancy.

This study provides important insights into the clinical characteristics, multi-disciplinary management, fetal and maternal outcomes of pregnancy-associated PE. Moreover, the rates of bleeding in this population treated predominantly with LMWH were consistent with similar studies. The use of anti-Xa was limited in this study, particularly in those with a high BMI and this warrants future research.

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APPENDICES

APPENDIX A: Data Collection Sheet

DATA COLLECTION SHEET

STUDY NO:

DATE:

DEMOGRAPHICS

Age Ethnicity

Parity Gravidity Miscarriages

Weight (kg) Height (cm) BMI (kg/m^2)

□ Smoker (> 10 cigarettes per day)

MEDICAL HISTORY

□ HIV- Diagnosis date □ ART

□ Hypertension- □ Gestational □ Chronic □ Pre-eclampsia

□ Diabetes- □ Gestational □ Type 1 □ Type 2

□ Active malignancy

□ Surgery or lower limb fracture within 1 month

□ Other

DRUG HISTORY

□ Thromboprophylaxis- Prophylactic Dose Therapeutic Dose

□ Aspirin use Indication Dose

□ Other

RISK FACTORS

ANTEPARTUM RISK FACTORS

□ Previous VTE- □ Unprovoked □ Provoked □ Pregnancy related

Diagnosis date: Treatment: Duration of treatment:

□ Family history of VTE

□ Medical co-morbidities

□ Gross varicose veins

□ Current systemic infection or peri-operative infection

□ Immobility

□ Multiple pregnancy

□ Dehydration/hyperemesis

POSTPARTUM RISK FACTORS

□ Readmission or prolonged admission (≥ 3 days) postpartum

□ Surgery in the puerperium

□ Prolonged labour (>24hours)

OBSTETRIC HISTORY

Delivery

Gestational age Birth weight (baby)

□ Scheduled delivery

Mode of delivery-□ CD □ Emergency Indication: □ Elective Indication:

□ NVD □ Assisted NVD

□ Anaesthesia- □ Spinal □ GA

Birth Outcome- □ Live Birth □ Stillbirth

Blood loss at delivery (ml)

□ transfusion required

□ placenta praevia

□ wound infection

Last dose of anticoagulation hours Re initiation of anticoagulant hours

Time interval from last dose to re-initiation

□ Contraception Postpartum

CLINICAL PRESENTATION:

Gestational Age

Gestational age estimated by: □ Early US □ Symphysis fundal height □ LMNP

Symptoms:

□ Chest pain

□ Shortness of breath

□ Palpitations

□ Haemoptysis

Other:

□ Symptoms of DVT:

Clinical signs:

HR (rpm) BP (mmHg) GCS SPO2 (%)

RR (rpm) Temp (°C)

□ Signs of DVT

INVESTIGATIONS

□ ECG

□ CX-Ray

□ VQ scan

□ CTPA- □PE Present □No PE □Inconclusive

□Segmental □Subsegmental □Lobar □Proximal

Pulmonary trunk size □< 30mm □≥ 30mm

□ Compression ultrasound

□ Echocardiogram- TAPSE Pulmonary pressure Right ventricle systolic function

MANAGEMENT

□ OPD

□ High care inpatient Length of stay

□ ICU inpatient Length of stay

□ General ward inpatient Length of stay

LMWH- Dose Duration

□ Anti Xa adjusted □ Weight adjusted

Warfarin- Dose

DOAC Dose

Duration □ 3 months □ 6 months □ 9 months □ Lifelong

□ Thrombolysis

COMPLICATIONS

□ Local skin reactions □ Bruising at injection site

Other:

□ Treatment changes due to drug hypersensitivity

□ CTPH Date

□ PTS Date

OUTCOMES

Date of diagnosis Last follow up date Date of death/bleeding/recurrent VTE

□ Demised: Date/Gestational age

□ Recurrent thrombosis Date Diagnosis

Bleeding: Antepartum and Secondary Post-Partum

□ Major □ CRNMB □ Minor

Primary postpartum

□ Major □ CRNMB □ Minor

LABORATORY INVESTIGATIONS:

	Date:		Date:	
HIV Viral load CD4 Count				
FULL BLOOD COUNT White Cell Count HB Platelet count Pre LMWH Platelet count Post LMWH				
Troponin				
eGFR				
D-dimer Presentation: At end of treatment:				
Antepartum Anti-Xa Dose of LMWH Weight Gestational age				
Postpartum Warfarin: INR INR INR TTR				
Thrombophilia screen	Yes		No	
Inherited Thrombophilia	Yes		No	
Thrombophilia type				
  APLS screen LAC Anti-CL IgG IgM aB2gp IgG IgM	Presentation Positive Positive Positive Positive Positive	 Negative Negative Negative Negative Negative	>12 weeks Positive Positive Positive Positive Positive	 Negative Negative Negative Negative Negative

APPENDIX B Antepartum and postpartum VTE risk assessment tool (12)

Table 2. Obstetric antepartum thromboprophylaxis risk assessment[4-8]

Risk Category	Recommendation
High Risk	
Previous unprovoked or pregnancy or oestrogen-related VTE	Antepartum Thromboprophylaxis indicated
High-risk hereditary thrombophilia (compound heterozygous or homozygous for Factor V Leiden or prothrombin gene mutation and some deficiencies of antithrombin)[19] and a positive family history of VTE*	
Anti-phospholipid syndrome and previous VTE	
Intermediate Risk	
Single VTE related to a transient risk factor (not related to pregnancy or oestrogen use)	Clinical monitoring indicated
Low and intermediate risk hereditary thrombophilia (some antithrombin deficiencies, Protein S deficiency, Protein C deficiency; heterozygous for Factor V Leiden or prothrombin gene mutation) [19] and a positive family history of VTE*	
High risk hereditary thrombophilia and no positive family history of VTE	Consider thromboprophylaxis
Antiphospholipid syndrome	
Non-obstetric surgery during pregnancy	
Medical co-morbidities, e.g. cancer, heart failure, peripartum cardiomyopathy, active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type 1 diabetes mellitus with nephropathy, sickle cell disease, current intravenous drug user	
Ovarian hyperstimulation syndrome (3 months after resolution)	
Low Risk	
Age >35 years	Early mobilisation and avoid dehydration
BMI ≥30 kg/m²†	
Parity ≥3	
Smoker (at least 10 cigarettes per day)	Thromboprophylaxis if multiple (>4) risk factors are present
Family history of unprovoked or oestrogen-related VTE in first-degree relative	
Low-risk thrombophilia	
Gross varicose veins‡	
Current systemic infection or peri-operative infection	
Immobility, e.g. paraplegia, long-distance travel (>8 hours), strict bedrest ≥7 days	
Pre-eclampsia with intrauterine growth restriction	
Multiple pregnancy	
In vitro fertilisation	
Dehydration/hyperemesis	

*A positive family history of VTE is associated with a two- to fourfold increase in the risk of VTE.
†The patient's BMI is based on the booking weight.
‡Gross varicose veins are by definition symptomatic, above the knee or associated with phlebitis or oedema or skin changes.

Table 3. Obstetric postpartum thromboprophylaxis risk assessment[4-8]

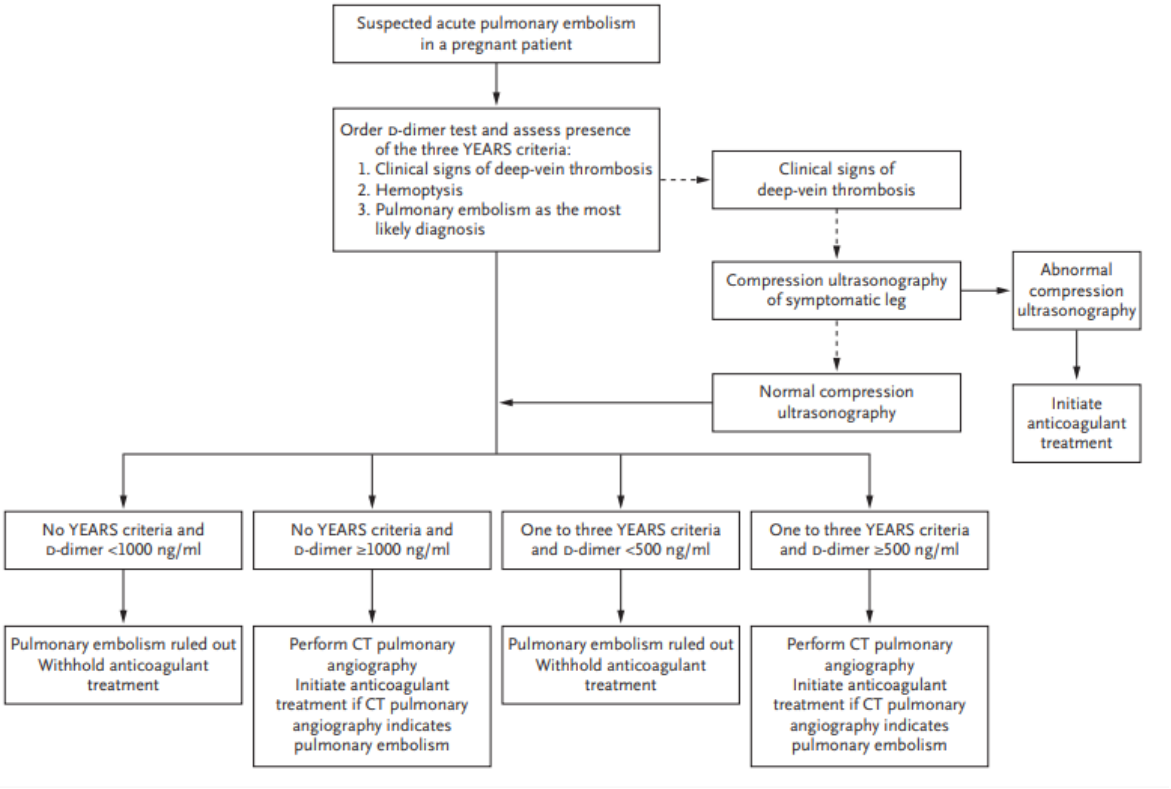
Risk Category	Recommendation
High Risk	
Anyone requiring antenatal LMWH Previous VTE High-risk hereditary thrombophilia (compound heterozygous or homozygous for Factor V Leiden or prothrombin gene mutation or some deficiencies of antithrombin) Low- and intermediate-risk (some antithrombin deficiencies, Protein S deficiency, Protein C deficiency, heterozygous for Factor V Leiden or prothrombin gene mutation) hereditary thrombophilia and positive family history of VTE* Antiphospholipid syndrome	Postpartum thromboprophylaxis indicated for at least 6 weeks
Intermediate Risk	
Caesarean delivery in labour Readmission or prolonged admission (≥ 3 days) postpartum Surgery in the puerperium (except immediate repair of the perineum) Medical co-morbidities e.g. cancer, heart failure, peripartum cardiomyopathy, active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease, nephrotic syndrome, type 1 diabetes mellitus with nephropathy, sickle cell disease, current intravenous drug user BMI ≥40 kg/m^2†	Postpartum thromboprophylaxis indicated for at least 7 - 10 days If risk factors persist or multiple (≥2) risk factors are present, consider extending thromboprophylaxis
Low Risk	
Age >35 years BMI ≥30 kg/m^2 Parity ≥3 Smoker Elective caesarean delivery Family history of VTE Low-risk thrombophilia Gross varicose veins‡ Current systemic infection Immobility, e.g. paraplegia, long-distance travel (>8 hours) Multiple pregnancy Preterm delivery in this pregnancy (<37 weeks) Stillbirth in this pregnancy Mid-cavity or rotational operative delivery Prolonged labour (>24 hours) Postpartum haemorrhage (> 1 L or blood transfusion requiring re-operation)	Early mobilisation, mechanical prophylaxis§ and avoid dehydration Postpartum thromboprophylaxis at least until discharge from hospital if multiple (≥ 2) risk factors

*A positive family history of VTE is associated with a two- to fourfold increase in the risk of VTE.
†The patient's BMI is based on the booking weight.
‡Gross varicose veins are by definition symptomatic, above the knee or associated with phlebitis or oedema or skin changes.
§Mechanical prophylaxis includes intermittent pneumatic compression which is preferable to graduated compression stockings.

APPENDIX C Revised Geneva Score for Pulmonary Embolism(18)

Pregnancy-Adapted Geneva Score	
ITEM	**POINTS**
Age 40 years and older	+1
Surgery (under GA) or lower limb fracture in past month	+2
Previous DVT or PE	+3
Unilateral lower limb pain	+3
Hemoptysis	+2
Pain on lower limb palpation and unilateral edema	+4
Heart rate >110 bpm	+5
Maximal point number	20
ROC curve AUC	0.795
95% CI	0.690–0.899

APPENDIX D Pregnancy Adapted YEARS algorithm (19)



APPENDIX E ISTH-SCC bleeding risk assessment tool (25)

TABLE 3 Proposed classification for antepartum and secondary postpartum (24 h to 6 wk after delivery) periods: colors correspond to the criteria selected for each class of bleeding: red for major bleeding, orange for clinically relevant nonmajor bleeding, and green for minor bleeding, respectively

		Major bleeding	CRNMB	Minor bleeding
Antepartum and secondary postpartum periods				
Vaginal bleeding	Prompting a face-to-face evaluation			
	Leading to hospitalization			
	Leading to antithrombotic therapy modification			
	Related to early pregnancy loss[c]			
Placenta praevia				
Placenta abruption				
Fetal or neonatal death (for example bleeding because of placenta abruption)				
Any sign or symptom of hemorrhage[c] including bleeding found by imaging alone				
	Prompting a face-to-face evaluation			
	Leading to hospitalization or increased level of care			
	Requiring medical intervention by health-care professional			
Acute clinically overt bleeding				
	Leading to death			
	That occurs in a critical organ: intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intra-articular, intramuscular with compartment syndrome			
	Associated to a fall in hemoglobin level of 2 g/dL or more			
	Leading to transfusion of two or more units of whole blood or red cells to			

[a]Early pregnancy loss before the 13th gestational week (first trimester).

[b]Placenta praevia requiring delivery.

[c]Defined as any overt, actionable sign of hemorrhage (vaginal and nonvaginal) that does not fit the criteria of major bleeding (including spontaneous subcutaneous hematoma >25 cm^2 or >100 cm^2 if provoked).

TABLE 4 Proposed classification for primary postpartum (first 24 h of delivery) period: colors correspond to the criteria selected for each class of bleeding: red for major bleeding, orange for clinically relevant nonmajor bleeding, and green for minor bleeding, respectively

		Major bleeding	CRNMB	Minor Bleeding
Primary postpartum period[a]				
Blood loss <1000 mL	Alone (including one prophylactic administration of uterotonics)			
Leading to	Uterus intervention to stop bleeding (eg curettage)			
	A first line of treatment with uterotonics and/or tranexamic acid			
	Transfusion of two or more units of whole blood or red cells to maintain hemoglobin level >7-9 g/dL			
Blood loss ≥1000 mL	Alone			
Leading to				
	A first line of treatment with uterotonics and/or tranexamic acid			
	Uterine intervention to stop bleeding (eg curettage)			
	A second line of treatment with uterotonics			
	Transfusion of two or more units of whole blood or red cells to maintain hemoglobin level >7-9 g/dL			
	Balloon tamponade			
	Embolization			
	Conservative surgery			
	Hysterectomy			
	Death			

APPENDIX F Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

30 September 2024

Drs NC Zulu, J Zamparini and H Rhemutla
School of Pathology
Department of Molecular Medicine and Haematology
Medical School
University

Sent by e-mail to: Candice.Zulu@nhls.ac.za

Dear Dr Zulu

Protocol Ref No: M221187
Protocol Title: *Clinical presentation, management and outcomes of pulmonary embolism in pregnancy at Charlotte Maxeke Johannesburg Academic Hospital*
Principal Investigators: Drs NC Zulu, J Zamparini and H Rhemutla

Thank you for your letter of 25 September 2024.

I confirm that we have noted and approve of your proposal to extend your data collection to include all records up to and including 30 September 2024.

Thank you for keeping us informed.

Yours Sincerely

J. Burns

.....
Mr I Burns, for the Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:

Drs NC Zulu, J Zamparini and H Rhemutla
School of Pathology
Department of Molecular Medicine and Haematology
Medical School
University

E-mail: Candice.Zulu@nhls.ac.za

CC:

Supervisor: Professor E Schapkaitz
<Elise.Schapkaitz@nhls.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM:

Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/02/14

REF: R14/49

PROTOCOL NO: **M221187** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Clinical presentation, management and outcomes of pulmonary embolism in pregnancy at Charlotte Maxeke Johannesburg Academic Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Drs NC Zulu, J Zamparini and H Rhemutla

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M221187

NAME: (Principal Investigator)	Drs NC Zulu, J Zamparini and H Rhemutla
DEPARTMENT:	School of Pathology Department of Molecular Medicine and Haematology Medical School University
PROJECT TITLE:	*Clinical presentation, management and outcomes of pulmonary embolism in pregnancy at Charlotte Maxeke Johannesburg Academic Hospital*
DATE CONSIDERED:	2022/11/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professor E Schapkaitz
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/02/14

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

16/02/2023
Date

APPENDIX G Similarity Report

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