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A Review of the Use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre

Dr Wilhelm Herbst

671874

Supervisors: Dr Jarrod Zamparini, Dr Halvani Moodley, Dr Shastra Bhoora

A research project submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Master of Medicine (MMed) in Internal Medicine

i. DECLARATION

I, Wilhelm Herbst declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine (MMed) in Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



Wilhelm Herbst

On this 23th day of April 2024

ii. DECLARATION: STUDENT'S CONTRIBUTION TO ARTICLE(S) AND AGREEMENT OF CO-AUTHOR(S)

I, Wilhelm Herbst, student number 671874, declare that this Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Research Report .

Signature of Student:………….**Date**: 23rd April 2024.

Name of Primary Supervisor: Dr Jarrod Zamparini

Signature of Primary Supervisor .....**Date**.....

Article 1: Title: A Review of the Use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre.

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iii. PUBLICATIONS AND PRESENTATIONS

This research project has been prepared in the format for a submissible article according to the author guidelines as outlined by the journal *Obstetric Medicine*. This work has never been published nor presented at any congresses.

iv. LIST OF ABBREVIATIONS

ATS – American Thoracic Society

BMI – body mass index

sBP – systolic blood pressure

CRP – C-reactive protein

CTPA – computed tomography pulmonary angiography

CT – computed tomography

ECG - electrocardiogram

HIV – Human Immunodeficiency Virus

IQR – interquartile range

MMR – maternal mortality rate

MUAC – mid upper arm circumference

RCOG – Royal College of Obstetricians and Gynaecologists

SOGC – Society of Obstetricians and Gynaecologists of Canada

VL – viral load

VTE – venous thrombo-embolism

PACS – picture archiving and communicating system

PE – pulmonary embolism

PCT - Procalcitonin

PROM – premature rupture of membranes

V. ACKNOWLEDGEMENTS

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- My co-supervisors Professor Shastra Bhoora and Dr Halvani Moodley for their determination and meticulous assistance through every step.
- Dr Ashesh Ranchod, Dr Tracey Westgarth-Taylor and Dr Halvani Moodley for their time and effort to read the CTPA scans.

vi. DEDICATION

I dedicate this work to my wife Ilze and my son Joshua for their steadfast love and support. This would not have been possible without you.

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CHAPTER 1: RESEARCH PROTOCOL

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1.1 Introduction

Background

The most common cause of maternal death during pregnancy and the puerperium in developed countries is venous thromboembolic events, including pulmonary embolism (PE).[1] The risk for venous thromboembolism (VTE) is significantly increased during pregnancy and the postpartum period, as these patients are in a state of hypercoagulability, are prone to venous stasis and may have superimposed endothelial damage.[2]

Data has shown that women have a 5-fold increased risk of developing VTE during pregnancy, as compared to their non-pregnant counterparts,[3] and, according to a Scottish study, the incidence of antenatal VTE has increased over the last 26 years.[4] Past research has observed an incidence of PE in pregnant or postpartum women of 3 in 10,000[2,5], with one death in every 100,000 deliveries.[6] Some studies have found an absolute incidence of VTE in pregnancy to be as high as 1 to 2 cases per 1000 pregnancies[3]; a risk that is nearly five times higher than that among non-pregnant women.[7]

More than half the cases of VTE in pregnancy occur in the first trimester, before 20 weeks' gestation.[5] Yet, 80% of VTE cases in the postpartum period have been observed to occur within the first 3 weeks following delivery.[8] Recent studies have revealed a raised relative risk (however low absolute risk) that remains up to 12 weeks following delivery.[9]

A large meta-analysis and systematic review of seventeen studies, which included 25,339 patients, found that 2% of patients presenting to the emergency department with symptoms suggestive of PE, were pregnant.[10] This translates to a 12.4% positivity rate for VTE in nonpregnant patients, compared with 4.1% in pregnant patients.[10] The perceived lower yield of confirmed VTE in pregnancy can be ascribed to the low threshold physicians have to scan pregnant patients, due to the high risk of devastating sequelae of PE in pregnancy.[10]

Risk Factors

The clinical presentation of VTE may be masked by the characteristic symptoms of pregnancy such as peripheral pedal oedema, along with an increased respiratory rate and mild tachycardia.[11] Pregnancy presents certain risk factors to hypercoagulability

including immobility in late pregnancy, iliac compression by the gravid uterus, and dehydration secondary to nausea and vomiting (which affects 50-90% of pregnant women[12]), hypercoagulability (resulting from increased concentration of certain clotting factors as well as a decrease in endogenous anticoagulants such as antithrombin and protein S)[12], endothelial injury resulting from delivery trauma and venous distension[12,13] as well as thrombophilia.[14]

Certain non-modifiable risk factors associated with thrombosis such as Human Immunodeficiency Virus (HIV)[15], Antiphospholipid syndrome (APS)[16] and Obesity[17] must also be taken into account as these pre-existing conditions may be encountered in pregnancy. Gestational diabetes and multiple gestations have not been proven to be significantly associated with an increased risk for thrombosis.[18]

There are a number of postpartum factors which have been associated with an increased risk of VTE, such as surgical delivery, particularly in the emergency setting or during prolonged labour, post-partum haemorrhage, thrombophilia, pre-eclampsia, and puerperal sepsis.[14]

Normal physiological changes in pregnancy can overlap with clinical manifestations of VTE which deems the diagnosis of PE exceptionally difficult, in addition the accuracy of diagnostic imaging is notably compromised by the hyperdynamic circulatory state in pregnancy.[19] Most studies have generally disregarded the pregnant population when investigating the diagnosis of PE.[20]

Clinical predictors

Certain clinical predictors of PE, such as active malignancy or advanced age are less relevant in the pregnant population. The Wells' criteria includes tachycardia and lower limb oedema, both of which occur commonly in pregnancy, lowering the specificity in these patients.[21] Consequently, considering an alternative diagnosis to PE will be more challenging to establish in pregnancy.[21] The recommendations outlined by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the Royal College of Obstetricians and Gynaecologists (RCOG), advocate against clinical predictors to assess VTE in pregnant women, whilst other guidelines omit instruction in this regard.[23]

A recent Irish study that included 103 pregnant and post-partum participants from a single tertiary maternity establishment, who underwent CTPA for the suspicion of PE, observed that none of these women with a retrospectively assigned Wells' score of 6 or less confirmed a diagnosis of PE, yielding a very significant negative predictive value of 100% (95% confidence interval not stipulated).[24] A comparable British study that was conducted with 183 pregnant women with suspected PE, all referred for ventilation perfusion (V/Q) imaging, established that PE was successfully excluded in all 107 participants with a modified Wells' score less than 5.[25]

D-dimer

In non-pregnant patients PE can be safely excluded in the presence of a normal D-dimer in addition to a low pre-test probability. It must conversely be interpreted with caution in patients with a high pre-test probability, as a falsely negative result can miss a diagnosis of PE.[20] Most of the related studies that ascertained the use and shortcoming of D-dimer in diagnosing PE, have not included pregnant women as participants.[26]

Van der Pol et al found that the pregnancy-adapted YEARS algorithm safely excluded acute PE in pregnant patients who were suspected to have PE, evidently this approach allowed CTPA to be avoided in 32 – 65% of patients, dependent on the trimester of pregnancy, without risking further harm.[27]

According to the guidelines outlined by the Society of Thrombosis and Haemostasis Research (GTH) and the European Society of Cardiology (ESC), a negative D-dimer can justify avoiding unnecessary imaging in pregnant women suspected to have a PE.[22,23] However the American Thoracic Society (ATS), SOGC, and RCOG recommendations state that a D-dimer should not be used in pregnancy to exclude the diagnosis of PE.[28] Several observational studies, evaluating the use of D-dimer to assess suspected DVT in pregnant women, revealed a high negative predictive value proposing that a negative D-dimer test using pregnancy-specific cut-offs may sufficiently exclude DVT in pregnancy.[27,29,30]

CT Pulmonary Angiography

There is no local data to evaluate the yield of CTPA in pregnant and postpartum patients, however accepted standards in the general population indicate CTPA should detect PE in 15.4 - 37.4% of patients and alternative diagnoses in up to 56%.[31]

A study done by Shahir et al found that 5.6% of pregnant women who underwent CTPA had nondiagnostic studies, a rate similar to that in the general non-pregnant population.[32] Certain physiological factors may influence the quality of CTPA such as increased circulatory volume and altered cardiac output, which effectively leads to lower pulmonary artery opacification.[32] Insufficient opacification of the pulmonary vasculature during CTPA is described twice as often among pregnant women compared to those who are not pregnant.[33] This may be explained by the increase in plasma volume with consequent dilution of contrast medium, in addition the hyperdynamic circulation in pregnancy results in contrast disruption when there is accelerated mixture of opacified blood from the superior vena cava and non-opacified blood from the inferior vena cava.[21] Evidently normal CTPA imaging in pregnancy, has been found to have a high negative predictive value.[34,]Given the higher radiation dose associated with CTPA, exposure to the maternal breast carries carcinogenic risk on account of the radiosensitive character of the glandular breast in pregnancy, and during lactation.[35] Hohl et al observed that CTPA can increase the risk of breast cancer by 1.5%[35], however recent studies have established that this risk is negligibly low[36] unless there is a family history of breast cancer.[37] Adaptions have been made to current CT protocols to ensure lower maternal and foetal radiation doses.[32,38]

A study by Jordan et al including 34 pregnant women, 16 postpartum women, and 50 age-matched controls, found that CTPA in pregnant patients had a significantly lower positivity rate than controls (2% compared to 16% respectively).[39] A 17-year retrospective study by Rotzinger et al done at a single center in Switzerland observed that CTPA rarely indicated PE in pregnancy, with an alternative diagnosis found in 30% of pregnant patients investigated.[40]

Other imaging modalities

Ultrasound and lower limb doppler in pregnant women with suspected PE are recommended by four international guidelines, however factors affecting the selection criteria of patients differ.[28,41,42] The GTH and ESC guidelines advocate for bilateral lower limb doppler for all pregnant women with a suspicion for PE, regardless of whether there are clinical evidence of DVT,[28,41] whilst the RCOG and ATS guidelines suggest that lower limb ultrasound only be used in pregnant patients who have clinical

evidence of DVT,[23] as the diagnostic yield of lower limb ultrasound is low when DVT symptoms are absent.

Despite the role for chest radiography in patients with suspected PE, it is neither sensitive nor specific.[21] Nevertheless, its role is vital as it can reveal other underlying pathologies that may provide an alternative explanation for the presenting symptoms.[21]In addition, V/Q imaging can only be accurately interpreted in the presence of a normal chest X-ray.[21]

Compared to ventilation/perfusion (V/Q) imaging, CTPA has been associated with an higher radiation dose to maternal breast tissue, but lower dose to the fetus.[43] The dose of radiation per maternal breast is 0.11 – 0.31 mGy in perfusion scanning[44], and 10 – 70 mGy in CTPA.[35] V/Q imaging and CTPA in pregnancy, have a similar yield of non-diagnostic results; 12.5% (95% CI 5.3 -19.6) and 11.5% (95% CI 7.5 – 18.4) respectively in a systematic review that evaluated 22 studies with a total of 2,391 imaging investigations (1,165 V/Q scan and 1,226 CTPA).[45] However, in South Africa, CT remains the primary diagnostic modality for PE given the limited number of Nuclear Medicine units and the relative ease of access to CT facilities. [46]

1.2 Aim of the study

PE is the leading cause of mortality in pregnant and postpartum patients worldwide, therefore physicians have a low threshold to investigate for it. International data established that CTPA is effective in detecting PE, as well as alternative diagnoses. In South Africa CTPA is considered the investigation of choice for PE, as VQ scanning is not available in most settings. There is however no local data to evaluate the yield of CTPA in pregnant and postpartum patients in South Africa. The aim of the study is to evaluate the yield of CTPA to diagnose PE in pregnancy and postpartum period in a South African context, and to compare clinical features in patients suspected to have PE in pregnancy and the postpartum period who underwent CTPA, as well as to ascertain the prevalence of alternative CT findings in patients without PE who underwent CTPA.

1.3 Research Question

In patients admitted to an Obstetric High Care unit what were the clinical characteristics of patients that underwent CTPA, what proportion of patients had a pulmonary embolus

and was there a difference in clinical findings in those with and without pulmonary embolus by CTPA?

1.4 Study Objectives

- To describe the clinical characteristics of patients that underwent CTPA and determine the proportion of patients undergoing CTPA that had a pulmonary embolus
- To compare the clinical features of those patients with PE to those without
- To ascertain the prevalence of alternative CT findings in patients without PE that underwent CTPA

1.5 Methods

Study Design

This study will be a retrospective cross sectional review.

Study Population

Pregnant and postpartum women admitted to the Obstetric High Care unit at Charlotte Maxeke Johannesburg Academic Hospital from 1 January to 31 December 2019, inclusive, who underwent CTPA.

Exclusion Criteria

- Patients who had a PE diagnosed by a method other than CTPA
- Patients referred from other institutions where imaging was performed elsewhere
- Patients with known PE, diagnosed prior to admission
- Patients who were not pregnant or not in the puerperium (period of 6 weeks following delivery)

Data Collection

Data will be collected from the following sources:

- The names and hospital numbers of all patients admitted to the Obstetric High Care Unit for the study period will be collected from the ward admission register.
- The names and hospital numbers above will be cross-referenced with the hospital PACS Radiology system to determine which patients underwent CTPA.
- The included patients will be anonymised and allocated a unique study number which corresponds to the included patient.

- The CTPA images which were done for the included patients will be reviewed and reported on by two radiologist to remove any interobserver bias that may exist in the interpretation of the CTPA results
- The files for the relevant patients will be collected from the archives department and clinical data as indicated on the data collection sheet (Appendix A) will be extracted.

Statistical Analysis

General Statistical considerations

This is a cross sectional retrospective analysis with the primary objective to describe the clinical characteristics of patients who underwent CTPA and to compare the clinical features of those patients with PE to those without. Data will be entered into a database which will then be used to perform statistical analysis. Descriptive statistics will be employed to analyse the data. Summary statistics with variables will include the mean, and standard deviation. Categorical variables will be presented as frequency counts and percentages. The data will be tabulated and analysed with respect to patient demographics, clinical features and laboratory investigations, and outcome of radiological investigations with appropriate statistical tests chosen depending on the distribution of data.

Analysis populations

The Obstetric High Care at CMJAH had 800 admissions in the 2019 calendar year. We anticipate, through estimations from the head of unit, that approximately 10% of these women would undergo CTPA during admission. Given this estimation and based on a 95% confidence level with a 5% margin of error we aim to include 66 women in our study population, where imaging will be reviewed and clinical characteristics will be tabulated and compared to the radiological findings.

Efficacy Analysis

Outcome of radiological imaging will be analysed. In view of the findings on imaging, the clinical characteristics of those patients with confirmed PE will be compared to those with PE excluded. The incidence of PE in patients who underwent CTPA will be compared to statistics from international data.

1.6 Limitations

- The retrospective design of the study places limitation on:

    - The availability of clinical data as all required data may not have been recorded,
    - The availability of radiological imaging as studies with suboptimal imaging will not be able to be repeated.
- The patient population is limited to admissions to the high care unit, however the majority of patients with suspected PE are managed in this unit.
- The imaging modality is limited to CTPA, excluding patients who received ventilation perfusion scans.
- This study will take place in a single healthcare centre, excluding patients from other centres.

1.7 Ethical approval

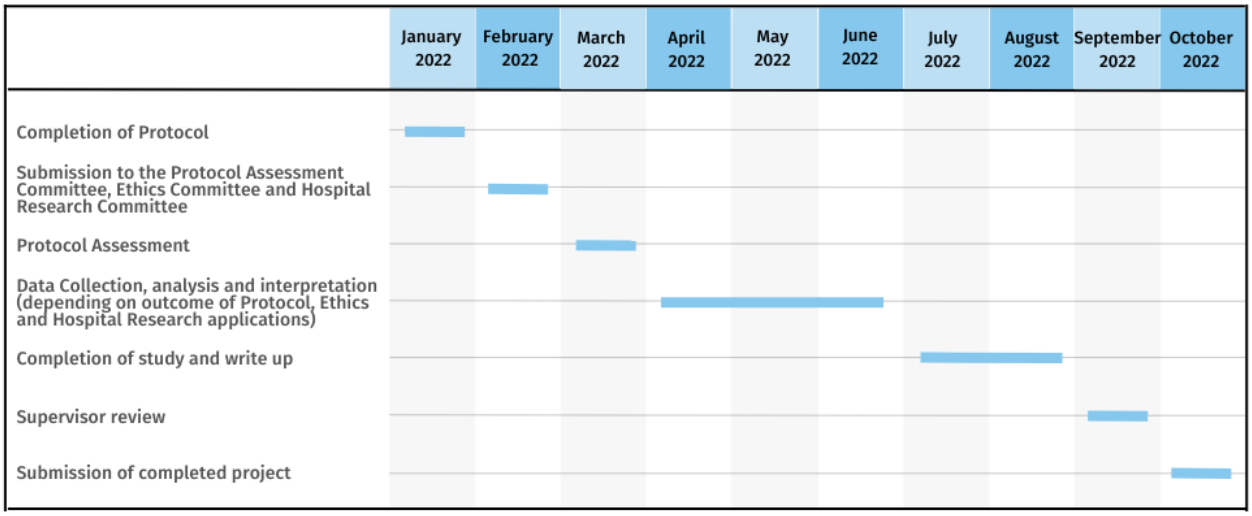
Ethical approval will be obtained from the Wits Human Research Ethics Committee (Medical). Permission to conduct the study at the research site will be sought from the Research Committee of Charlotte Maxeke Johannesburg Academic Hospital and the Heads of the Departments of Obstetrics & Gynaecology and Radiology, to access clinical and radiological data respectively. The study will also be registered with the National Health Research Database.

1.8 Funding

The preparation and printing costs will be self-funded, which will include the following:

- Stationery – R 1 500.
- Hard drive to contain imaging to be reviewed by Radiologist – R 1 500.

1.9 Timeline


January 2022
February 2022
March 2022
April 2022
May 2022
June 2022
July 2022
August 2022
September 2022
October 2022
Completion of Protocol
Submission to the Protocol Assessment Committee, Ethics Committee and Hospital Research Committee
Protocol Assessment
Data Collection, analysis and interpretation (depending on outcome of Protocol, Ethics and Hospital Research applications)
Completion of study and write up
Supervisor review
Submission of completed project

1.10 References

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APPENDIX A: Data Collection Sheet

Pulmonary embolism in Obstetric HCU													
Participant Number													
Demographics													
DOB				**Age**		**Gender**		F					
Race	Black		White		Coloured		Indian		Asian				
History													
Pregnant?	Yes		No		**Postpartum**		Yes		No				
Multiple Gestation	Yes		No										
Gestational Age			**Weeks Postpartum**										
Method (GA)	LNMP		Early US		**Mode of Delivery**		CS		NVD				
	Late US		Clinical				Assisted						
Obstetric Hx	Gravidity			Parity			Miscarriages						
Pregnancy Complications present?				Yes			No						
If yes, which:	Anaemia			Antepartum Haemorrhage			Chorioamnionitis						
(Can select more than one)	IUGR			Placenta Praevia			Preterm Labour						
	Preterm ROM			Preeclampsia			Eclampsia						
	HELLP			PPH			PIH						
	PPCMO			Gestational DM			Puerperal Sepsis						
				Relook Laparotomy									
	ICU Admission		Reason:										
	Other		What other:										
Medical History													
Autoimmune Disease				**Yes**		**No**		**Unknown**					
Antiphospholipid Syndrome				**Yes**		**No**		**Unknown**					

Chronic Kidney Disease	**Yes**		**No**		**Unknown**	
Chronic Lung Disease	**Yes**		**No**		**Unknown**	
Diabetes	**Yes**		**No**		**Unknown**	
Epilepsy	**Yes**		**No**		**Unknown**	
Heart Failure	**Yes**		**No**		**Unknown**	
HIV	**Yes**		**No**		**Unknown**	
Hypertension	**Yes**		**No**		**Unknown**	
Prev. Tuberculosis	**Yes**		**No**		**Unknown**	
Valvular Heart Disease	**Yes**		**No**		**Unknown**	
Previous VTE?	**Yes**		**No**		**Unknown**	
Comments / Elaborate						

Examination											
BP			**Pulse**			**Resp Rate**					
Height			**Weight**			**BMI**					
MUAC			**Saturation**								
CVS											
Resp											
Modified YEARS Algorithm | Score: _____											
Pregnant:	Yes				No						
Clinical signs of DVT:	Yes				No						
Haemoptysis:	Yes				No						
PE most likely dx:	Yes				No						
D-Dimer	< 0.5 mg/L		0.5 – 0.99 mg/L		> 1 mg/L						
Well's Score for PE | Score: _____											
Clinical signs and symptoms of DVT:				Yes (+3)		No (0)					
PE is #1 likely diagnosis OR equally likely:				Yes (+3)		No (0)					
Heart rate >100:				Yes (+1.5)		No (0)					
Immobilization at least 3 days OR surgery in the previous 4 weeks:				Yes (+1.5)		No (0)					
Previous, objectively diagnosed PE or DVT:				Yes (+1.5)		No (0)					
Haemoptysis:				Yes (+1)		No (0)					
Malignancy:				Yes (+1)		No (0)					
ECG Feat.	Right atrial enlargement (P pulmonale)		Sinus tachycardia		Clockwise rotation						
	$S_1Q_3T_3$ Pattern		Dominant R wave V1		Atrial tachyarrhythmias						
	Complete or incomplete RBBB		Right ventricular strain								
	Non-specific ST segment and T wave changes (including ST elevation and depression)										
Laboratory Data (within 24h of CTPA)											
FBC											
U&E											
D-Dimer		**CRP**			**PCT**						
Radiological Data											
CTPA	PE		No PE		Inconc.						
Distribution of PE	Proximal (Pulmonary Trunk/Pulmonary Artery)										

	Lobar (Interlobar Artery)					
	Segmental					
	Subsegmental					
Other CT Findings						
Pleural Effusion		Pneumothorax		GGO		
Consolidation		Cavitation		Bronchiectasis		
Atelectasis		Nodules		Masses		
Side:	Left		Right			
Comments (include location for each of the above findings)						

APPENDIX B: Letters to HOD

27/01/2022

Dear Prof. Chauke,

I wish to request permission to conduct research with patients from the Department of Obstetrics and Gynaecology, for the purpose of my MMed, titled A Review of the use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre.

The research will be supervised by Dr Shastra Bhoora (Dept Obstetrics & Gynaecology), Dr Jarrod Zamparini (Dept Internal Medicine), and Dr Halvani Moodley (Dept Radiology).

The participants will include admissions to the Obstetric High Care unit at Charlotte Maxeke Johannesburg Academic Hospital for the period January to December 2019. Access to patient files is requested.

Please find attached the protocol for the research project.

Your approval will be much appreciated.

Sincerely,



_____

Dr Wilhelm Herbst
Registrar: Internal Medicine

27/01/2022

Dear Prof. Ramaema,

I wish to request permission to conduct research with patients from the Department of Radiology, for the purpose of my MMed, titled A Review of the use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre.

The research will be supervised by Dr Halvani Moodley (Dept Radiology), Dr Jarrod Zamparini (Dept Internal Medicine), and Dr Shastra Bhoora (Dept Obstetrics & Gynaecology).

The participants will include admissions to the Obstetric High Care unit at Charlotte Maxeke Johannesburg Academic Hospital for the period January to December 2019, who received CT scans during this period. Access to PACS to review CT scans of study participants is requested.

Please find attached the protocol for the research project.

Your approval will be much appreciated.

Sincerely,



_____

Dr Wilhelm Herbst
Registrar: Internal Medicine

27/01/2022

Dear Prof. Chakane,

I wish to request permission to conduct research at Charlotte Maxeke Johannesburg Academic Hospital for the purpose of my MMed, titled A Review of the use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre.

The research will be supervised by Dr Shastra Bhoora (Dept Obstetrics & Gynaecology), Dr Jarrod Zamparini (Dept Internal Medicine), and Dr Halvani Moodley (Dept Radiology).

The participants will include admissions to the Obstetric High Care unit at CMJAH for the period January to December 2019. Access to patient files is requested.

Please find attached the protocol for the research project.

Your approval will be much appreciated.

Sincerely,



_____

Dr Wilhelm Herbst
Registrar: Internal Medicine

CHAPTER 2: MANUSCRIPT

This manuscript complies with the author guidelines for the journal *Obstetric Medicine* and has been formatted as such.

2.1 TITLE PAGE

A Submission to the journal Obstetric Medicine

Full Title: A Review of the Use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre

Short Title: CTPA in Pregnant and Postpartum Patients

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Informed Consent: Retrospective

Ethical Approval: The Wits Human Research Ethics Committee (Medical) approved this study (Clearance Certificate No. M220255)

Guarantor: WH

Authorship: WH and JZ conceived the study. SB assisted with data identification and retrieval. WH gained ethics approval, conducted the literature review, designed the data collection tool, collected raw data and wrote the first draft of the manuscript. HM, TWT and AR reviewed and reported all CT images. All authors contributed to the final manuscript.

Acknowledgements: We would like to thank all authors for their contribution.

Keywords: Pregnancy, VTE, CTPA

2.2 ABSTRACT

Background: Pulmonary embolism (PE), is a common cause of maternal death during pregnancy and the puerperium yet data on its prevalence in middle-income countries is lacking.

Methods: We examined the medical records and CTPAs of 67 women in an obstetric high care unit during pregnancy and the puerperium. We aimed to assess the efficacy of CTPA in diagnosing PE, evaluate associated clinical features, and determine the prevalence of alternative CT findings.

Results: CTPA detected PE in 11 women (16.42%) and alternative CT findings in 46 (68.6%). Women with PE had a significantly lower systolic BP than those without PE ($p = 0.001$). Multiple gestation, preterm rupture of membranes, and gestational diabetes were linked to higher PE prevalence.

Conclusions: This study, set in an upper middle-income country, demonstrated a higher CTPA yield for PE than in the international literature, emphasizing context-specific assessments.

2.3 INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE), is the most common cause of maternal death during pregnancy and the puerperium in developed countries.[1] The risk for venous thromboembolism (VTE) is significantly increased during pregnancy and the postpartum period, as these patients are in a physiological state of hypercoagulability, are prone to venous stasis and may have superimposed endothelial damage.[2]

Women have a 5-fold increased risk of developing VTE during pregnancy, as compared to their non-pregnant counterparts.[3] Globally, the incidence of PE in pregnant or postpartum women ranges from 1-2 per 1,000 to 3 per 10,000 deliveries [2,4], and one death in every 100,000 deliveries.[5] In South Africa PE accounted for 40 maternal deaths in 2022, with a maternal mortality rate of 4.1 per 100,000 live births.[6]

More than half of VTE cases in pregnancy occur before 20 weeks' gestation,[4] and 80% of VTE cases in the postpartum period occur within the first 3 weeks following delivery.[7]

Despite the increased risk of VTE in pregnancy, detection rates using CTPA (computed tomography pulmonary angiography) are lower in pregnant than non-pregnant women. A 2015 study found that 2% of pregnant women had a positive CTPA compared to 16% of non-pregnant women.[8] A 17-year retrospective study conducted at a single centre in Switzerland, published in 2020, observed that CTPA rarely indicated PE in pregnancy, with an alternative diagnosis found in 30% of pregnant women investigated.[9] Similarly, a 2023 study including 86 pregnant and 354 non-pregnant women investigated for PE by either CTPA or V/Q scan, noted positive scan rates of 3.5% and 8.8% in pregnant and non-pregnant women respectively.[10]

Risk Factors

Pregnancy is a hypercoagulable physiological state owing to an increased concentration of certain clotting factors as well as a decrease in endogenous anticoagulants such as antithrombin and protein S[11]. In addition, factors such as dehydration, secondary to nausea and vomiting in early pregnancy, immobility and iliac compression by the gravid uterus in late pregnancy, and endothelial injury from delivery trauma and venous distension[11,12] also play a role in the increased risk for VTE. The

clinical presentation of VTE may also be masked by “symptoms” of pregnancy such as pedal oedema, tachypnoea and tachycardia.[13] A number of postpartum factors are also associated with an increased risk of VTE, such as surgical delivery, particularly in the emergency setting or after prolonged labour, postpartum haemorrhage, thrombophilia, pre-eclampsia, and puerperal sepsis.[14]

Clinical predictors

The Wells’ criteria, which factors in tachycardia and lower limb oedema, is not particularly useful in pregnancy, given that these manifestations are frequently seen.[15] This complicates the differentiation of PE from other potential diagnoses in these women.[15] The recommendations outlined by the Society of Obstetricians and Gynaecologists of Canada (SOGC)[16] and the Royal College of Obstetricians and Gynaecologists (RCOG)[17], advise against clinical predictors to assess VTE in pregnant women.

D-dimer

In non-pregnant women PE can be safely excluded in the presence of a normal D-dimer in addition to a low pre-test probability. It must conversely be interpreted with caution in those with a high pre-test probability, as a falsely negative result can miss a diagnosis of PE.[18] The American Thoracic Society (ATS)[19], SOGC[16], and RCOG[17] recommendations state that a D-dimer should not be used in pregnancy to exclude PE as most studies investigating the use of D-dimer in diagnosing PE, have not included pregnant women as participants.[20]

Van der Pol et al found that the pregnancy-adapted YEARS algorithm safely excluded acute PE in pregnant women with suspected PE, allowing CTPA to be avoided in 32 to 65% of women.[21] A South African study found that the pregnancy-adapted YEARS algorithm successfully risk-stratified women in a single institution and would have reduced the number of CTPAs by 25.7% without missing any PE.[22]

CT Pulmonary Angiography

Accepted standards outlined by the Royal College of Radiologists state that CTPA should detect PE in 15.4 - 37.4% and alternative diagnoses in up to 56% in the general population.[23]

Most studies have disregarded pregnant women when investigating the diagnosis of PE.[18] Certain physiological factors, such as increased circulatory volume and altered cardiac output, may lead to lower pulmonary artery opacification influencing the quality of CTPA.[24] Insufficient opacification of the pulmonary vasculature during CTPA is described twice as often among pregnant women compared to those who are not pregnant.[25] Normal CTPA imaging in pregnancy, has been found to have a high negative predictive value.[26]

In this study we investigated the use of CTPA to diagnose PE in pregnant and postpartum women admitted to a high care setting in South Africa. We aimed to evaluate the prevalence of PE and alternative diagnoses as well as compare the clinical features of women with and without PE.

2.4 METHODS

We performed a cross-sectional analysis at the Charlotte Maxeke Johannesburg Academic Hospital, an academic centre in Johannesburg, South Africa. Pregnant and postpartum women admitted to the Obstetric High Care Unit (OHCU) between 1 January and 31 December 2019, who underwent CTPA for the suspicion of PE were consecutively enrolled in this study. We excluded women who had a PE diagnosed by a method other than CTPA, such as V/Q scan, due to limited availability in our setting. Women with imaging performed elsewhere, women with known PE diagnosed prior to admission, and women who were not pregnant or beyond 6 weeks post-delivery were also excluded.

The names and hospital numbers of all women admitted to the OHCU for the study period were collected from the ward admission register and cross-referenced with the hospital picture archiving and communicating system (PACS) to determine which women underwent CTPA. The included participant details were anonymised and allocated a unique study number. The CTPA images were reported on by two consultant radiologists (AR and TWT) who were blinded from each other's findings. The discrepant readings were reviewed by a third consultant radiologist (HM), also blinded from the findings of the other readers.

A final diagnosis was considered as agreement by two or more readers. Those studies with inconclusive findings or failing to achieve consensus among at least two readers, were interpreted as not having PE for the purposes of the study. The hospital files for the relevant participants were collected from hospital archives and clinical data was extracted. Data was captured in Microsoft Excel 16.78 (Microsoft Corporation, Redmond, USA) and statistical analysis was performed using Prism 10 (GraphPad Software Inc, La Jolla, CA, USA). Given the non-parametric nature of the data, the Mann-Whitney U test was employed for continuous variables, while the Fisher's exact test was utilized for categorical variables to determine significance.

2.5 RESULTS

A total of 732 women were admitted during the period under review, CTPAs were performed on 71 patients, of which 3 were not pregnant nor in the postpartum period and 1 had missing images, excluding them from the study, leaving a total of 67 women in the final analysis (Figure 1). The PE and non-PE groups were of similar age and race. The majority of the cohort were postpartum (82% in the PE group and 87.5% in the no PE group), and caesarean section was the most common mode of delivery in keeping with local trends. Most of the women were booked for antenatal care, and were multiparous. Table 1 provides demographic and pregnancy related data of the cohort.

Eleven women (16.4%) had a confirmed PE; 2 (18%) were pregnant and 9 (82%) postpartum and the majority (n=10, 90.9%) had peripheral PEs. Two women (18.2%) had a single embolism and 9 (81.8%) had multiple emboli.. The gestational age at delivery (in postpartum women) or time of scan (in pregnant women) was not significantly different ($p = 0.259$) in the non-PE group (median 34.5 weeks, IQR 30 – 38), compared to those with PE (median 30 weeks, IQR 26 – 38). Women with PE were more likely to have multiple gestation (27%) than without PE (4%) ($p = 0.028$). There was a larger proportion of women with alternative CT findings among those in the group with PE (n=9, 81.8%) compared to those without PE (n=37, 66.1%), yet the difference was not significant (p=0.481) (Table 2).

The difference in the technical adequacy of the CTPAs between the two groups was not significant ($p = 0.556$). This was assessed by measuring the opacification of the

pulmonary artery (Hounsfield units), between the two groups (median 237HU, IQR 216-277 versus median 247HU, IQR 209-285 in the PE and non-PE groups respectively). There was no difference in rate of motion artifact between the two groups (p = 0.492).

There was a significant difference in systolic blood pressure (sBP) between the two groups (p = 0.001) with lower sBP in the PE group (median 119mmHg, IQR 110 – 124) than in the non-PE group (median 134mmHg, IQR 120.3 - 146). There were no differences in other clinical features including the body mass index (BMI) or mid upper arm circumference (MUAC) between the two groups. Despite most women being tachycardic, there were no differences in electrocardiogram (ECG) findings between the two groups. It is not our standard protocol to analyse D-dimer routinely for the suspicion of PE in pregnancy, therefore only 27 women (40%) had D-dimers available. There was however no difference in D-dimers between the two groups (p = 0.219).

Biochemical inflammatory markers were available in a similar proportion of women, showing no difference between the groups, reflected by a median C-reactive protein (CRP) of 112mg/L in the PE group (10/11) and 100mg/L in the non-PE group (51/56) and a median procalcitonin (PCT) of 0.37ug/L in the PE group (8/11) and 0.31ug/L in the non-PE group. A diagnosis of puerperal sepsis was made in 36.4% in the PE group compared to 62.5% in the non-PE group, however the difference was not significant (p = 0.18). There were no other differences demonstrated in biochemistry between the two groups.

No women died in the non-PE group, while one woman died in the PE group (9%), however it is unclear if the death was directly caused by PE. Most women had a pregnancy-related complication, with the exception of 2 women (3.6%) in the non-PE group.

There were 2 women with HIV (18.2%) in the PE group, one of whom had a CD4 (CD4 = 464 cells/mm^3) and HIV viral load (VL = 764 copies/ml) available, whilst there were 17 women with HIV in the non-PE group (30.4%) where 15 had a CD4 result (median 344.5 cells/mm^3, IQR 269-457.75) and all had a viral load (n = 17, median 217 copies/ml, IQR 0 – 2472.25).

Gestational diabetes was significantly more prevalent (p = 0.042) among those with PE (n = 1, 9.1%) compared to those without PE (n = 2, 3.6%), as was premature rupture of membranes (PROM) (p = 0.025) comparing the PE group (n = 2, 18.2%) to the non-PE group (n = 0, 0%). There were no other complications or comorbidities with a significant difference between the groups (Table 3).

The Wells' score showed no correlation to PE, as all 67 (100%) women had a Wells' score of at least 4.5 (high risk for PE). When analysing the utility of the YEARS score [27], 7 women in the PE group and 20 women in the non-PE group had a D-dimer result available allowing the YEARS Score to be calculated. All 7 (100%) women in the PE group had a positive YEARS score, while 17 (85%) women in the non-PE group had a positive YEARS score. The difference was not significant (p = 0.545) (Figure 2).

2.6 DISCUSSION

In our study CTPA detected PE in 16.42% and alternative CT findings in 68.6% of our cohort, which is higher than reported in international literature. A large meta-analysis and systematic review of seventeen studies, including 25,339 women, found a 12.4% positivity rate for VTE in nonpregnant women, compared with 4.1% in pregnant women.[28] The high positivity rate in our cohort may be attributed to only including women admitted to a high care unit, assigning them to a higher risk category than other pregnant and postpartum women.

No clinical or biochemical biomarkers predicted PE in our cohort, similar to an Australian study evaluating the use of CTPA and V/Q in pregnancy and the puerperium.[29] The use of algorithms such as the modified YEARS and Wells' scores were limited in our cohort and would have been of no utility in reducing the number of CT scans done. However given our limited sample size, future studies are needed to further assess their utility in our setting. This is in keeping with recommendations from RCOG to avoid the use of clinical prediction tools in assessing VTE in pregnancy.[17]

Despite international guidelines considering maternal age over 35 years a risk factor for PE there was no significant difference in the age of the PE and the non-PE groups in our cohort.[30] There is evidence from the UK[31] and USA[32] that Black, Asian and minority ethnicities (BAME) have a much higher maternal mortality rate (MMR), with

the highest among Black women. There is evidence that PE is more prevalent in black ethnicities,[33] with a higher disease severity compared to other ethnicities.[34] The majority of our cohort were of Black ethnicity, making it difficult to compare outcomes related to ethnicity and to assess whether disparities exist.. This emphasises the importance of the high risk in this group, and the need for further research in a South African context

Caesarean delivery rate in the South African private sector was 73.2% in 2015[35], and increased from 15.1% in 2006[36] to 31.1% in 2022[6] in the public sector. Caesarean delivery is not done on maternal request in the South African public sector. Compared to the UK, the rate of caesarean delivery was 29%[31] in Wales, 31%[31] in England and 35%[31] in Scotland between 2019 - 2021. South African data shows that pregnant women who die from PE are more likely to have had a caesarean delivery.[37] In our cohort all women in the PE group were delivered by caesarean section, although this was for obstetric indications and not due to PE. While Caesarean delivery is a known risk factor for the development of PE[38], this was not demonstrated in our cohort and mode of delivery was not a risk factor for PE.

The most significant obstetric complication in our cohort was PROM with a higher prevalence in those with PE (n = 2, 18.2%) compared to those without PE (n = 0, 0%) (p = 0.025). Both women with PROM in the PE group were HIV positive, developed puerperal sepsis and had undergone caesarean delivery by gestational age of 28 and 35 weeks respectively. Only one of these women had a CD4 (CD4 = 464 cells/mm^3) and HIV viral load (VL = 764 copies/ml) available, and neither had a history of previous tuberculosis. PE was diagnosed after delivery in both women. The development of PE in these women was likely multifactorial however prolonged bed rest prescribed for the treatment of PROM was associated with an increased risk for PE in a study by *Kovacevich et al* (16.5 cases per 1000 compared to 0.8 per 1000 among pregnant women for whom this therapy was not prescribed).[39]

Systolic BP was significantly lower (p = 0.001) in the PE group, as was seen in the DiPEP study, however there were no differences in diastolic BP and heart rate. Out of keeping with the lower systolic BP in the PE group is that majority of these were peripheral PEs. However 81.8% of the women with PE had multiple emboli which may have contributed to the lower systolic BP. Hypotension associated with PE is attributed

to acute right ventricular dilatation compromising left ventricular filling and reducing cardiac output. Right ventricular dysfunction seen on echocardiography has been shown to correlate with pulmonary arterial obstruction of >30%, which is expected to occur with a large central PE[40]. Echocardiography was not available to assess for right ventricular strain, however there were no ECG features to suggest this.

The high prevalence of alternative findings on CTPA may be explained by the hospital's protocol for investigating PE, where CTPA is warranted if the chest X-ray is abnormal. Despite there being no significant difference in prevalence of alternative CT findings between women with PE and women without PE, the high burden of alternative findings on CTPA in women with PE could signify underlying pathology contributing to development of PE. The high prevalence of pregnancy related complications in our cohort is due to it consisting only of women in a high care setting.

Multiple gestation was a risk factor for PE in our cohort ($p = 0.028$) in keeping with guidelines from RCOG[17]. Gestational diabetes has not been proven to be associated with an increased risk for thrombosis[41], however was associated with PE in our cohort ($p = 0.042$). Despite HIV[42], antiphospholipid syndrome[43], and obesity[44] known to be associated with increased risk for PE, none were significant risk factors in our cohort.

The strengths of this analysis are driven from the racial representation in our cohort, largely consisting of Black African women, an underrepresented group in other studies, which underpins the need and potential for further research. Additionally, the data investigated were largely complete, all the CTPAs in our cohort contained adequate quality images, and were reviewed by consultant radiologists. Yet, the findings of this analysis must be interpreted in the context of some limitations. The first being, the small sample size. Considering our study was performed at a single centre including only women admitted to a high care setting, this in itself might be a major contributory factor to the high PE burden in our population, as these women were all in a higher risk category by nature of their condition. Another limitation is that chest radiographs were not reviewed, as this could have contributed to analysing the pre-test probability for PE.

2.7 CONCLUSION

PE remains a significant contributor to morbidity during pregnancy and the puerperium. While clinical and laboratory features were not reliable to exclude PE in our cohort, it is justifiable to consider CTPA when suspecting PE in this population, considering the higher detection rate compared to international literature. CTPA has a good yield for diagnosing PE and unmasking alternative diagnoses in a middle-income country setting. The presence of a low systolic blood pressure, multiple gestation, PROM, and gestational diabetes should raise the suspicion for PE in a high care setting. Prospective studies evaluating the use of d-dimer and scoring systems to predict PE in our population are warranted.

2.8 DECLARATIONS:

A Submission to the journal Obstetric Medicine

Full Title: A Review of the Use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre

Short Title: CTPA in Pregnant and Postpartum Patients

Authors:

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   Obstetric Internal Medicine Unit, Charlotte Maxeke Johannebsurg Academic Hospital and Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg

Declaration of Interests: The authors declare no conflicting interests

Funding: This research received no specific grant or funding

Informed Consent: Retrospective

Ethical Approval: The Wits Human Research Ethics Committee (Medical) approved this study (Clearance Certificate No. M220255)

Guarantor: WH

Authorship: WH and JZ conceived the study. SB assisted with data identification and retrieval WH gained ethics approval, conducted the literature review, designed the data collection tool, collected raw data and wrote the first draft of the manuscript. HM, TWT and AR reviewed and reported all CT images. All authors contributed to the final manuscript.

Acknowledgements: We would like to thank all authors for their contribution.

Keywords: Pregnancy, VTE, CTPA

2.9 TABLES AND FIGURES:

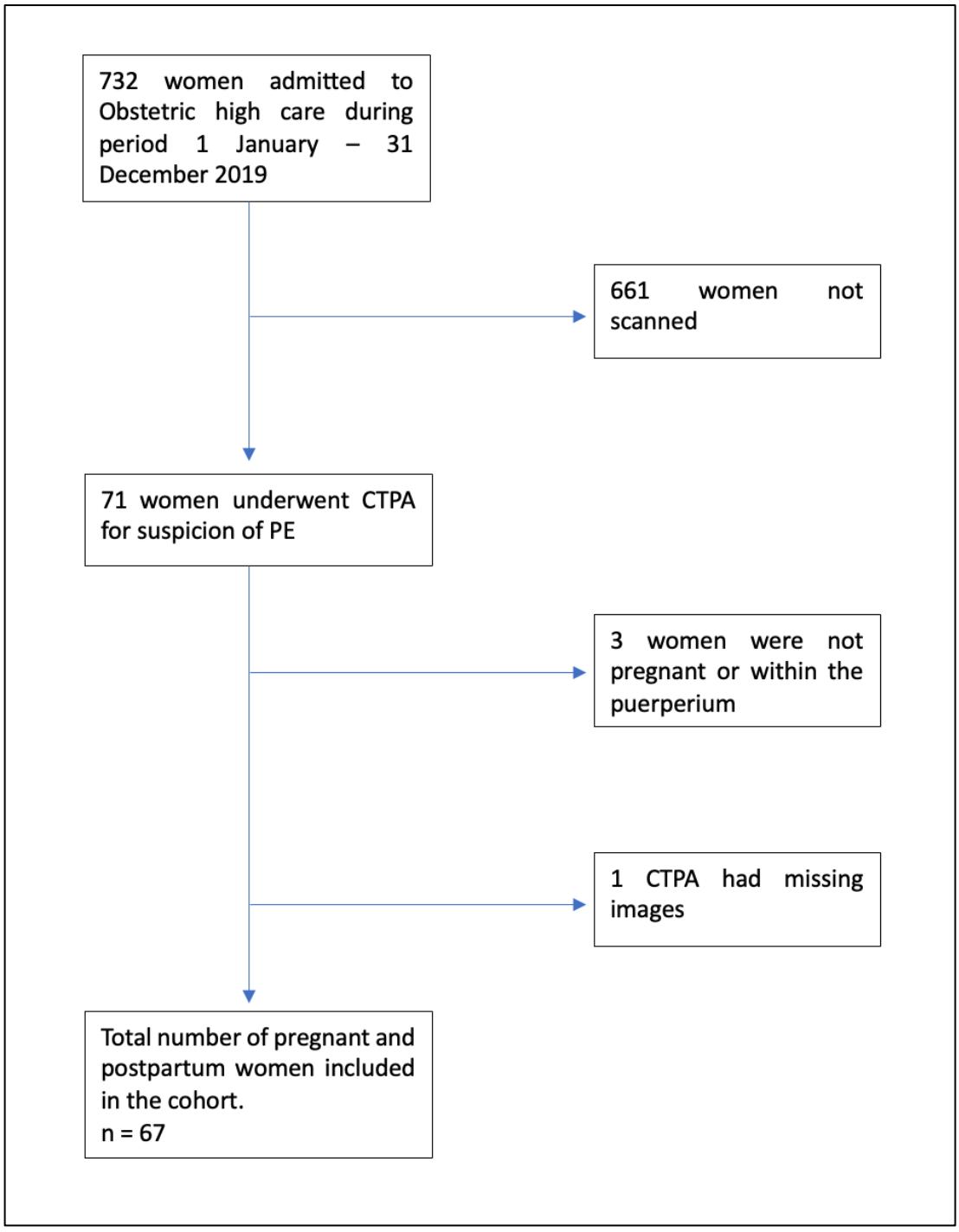

Figure 1: Study population

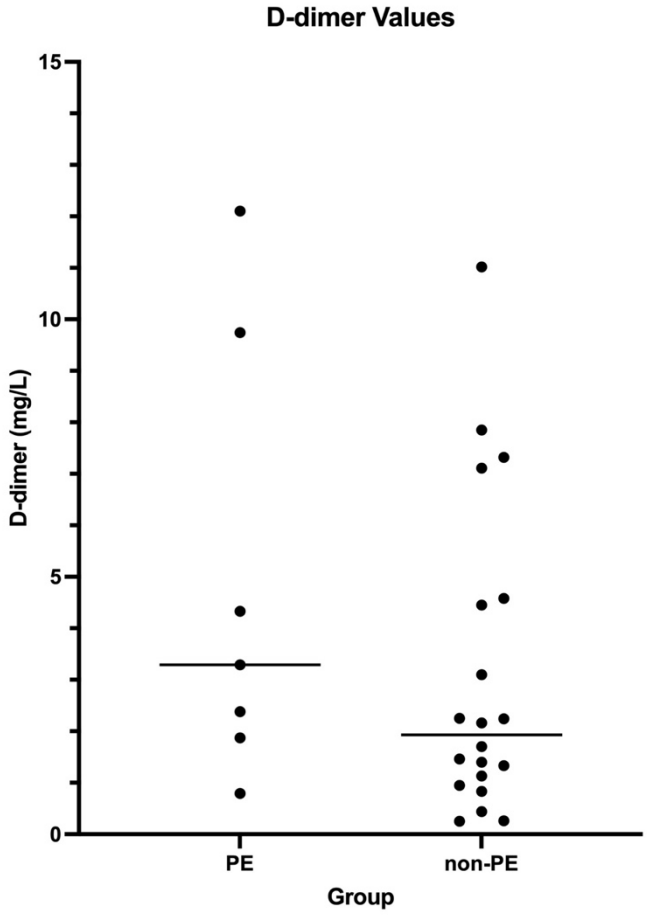

Figure 2: D-dimer values

Table 1: Demographics and pregnancy details

Demographics	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
Age (years), median, (IQR)	29 (26 – 35)	30 (26 – 33,75)	0.977
18 – 25	2 (18.18%)	12 (21.43%)	0.992
26 - 30	4 (36.36%)	18 (32.14%)	
31 - 35	3 (27.27%)	16 (28.57%)	
>35	2 (18.18%)	10 (17.86%)	
Race	PE, n (%)	No PE, n (%)	p-value
Black African	11 (100%)	55 (98%)	>0.999
White	0 (0%)	1 (2%)	
Pregnancy Details	PE, n (%)	No PE, n (%)	p-value
Postpartum	9 (82%)	49 (87.5%)	0.635
Pregnant	2 (18%)	7 (12.5%)	
Multiple gestation	3 (27%)	2 (4%)	0.028
Booked for antenatal care	8 (73%)	45 (80%)	0.686
Not booked for antenatal care	3 (27%)	11 (20%)	
Gestational age at delivery or time of scan (weeks), median (IQR)	30 (26 – 38)	34,5 (30 – 38)	0.259
Caesarean section	9 (82%)	41 (73.2%)	0.334
Normal vaginal delivery	0 (0%)	8 (14.3%)	
Gravidity (number of pregnancies), median (IQR)	3 (1 – 3)	2 (1 – 3)	0.971
Parity (number of live births) , median (IQR)	2 (1 -3)	2 (1 – 3)	0.714
Previous miscarriages (number), median (IQR)	0 (0 – 0)	0 (0 – 0)	0.841

Table 2: Alternative CT findings

CT findings	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
Pleural effusion	4 (36.4%)	14 (25%)	0.469
Ground glass opacification	6 (54.5%)	16 (28.6%)	0.157
Consolidation	3 (27.3%)	11 (19.6%)	0.686
Cavitation	0 (0%)	1 (1.8%)	>0.999
Bronchiectasis	0 (0%)	2 (3.6%)	>0.999
Atelectasis	8 (72.7%)	24 (42.9%)	0.101
Nodules	0 (0%)	5 (8.9%)	0.582

Table 3 YEARS score

YEARS score	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
YEARS positive	7 (100%)	17 (85%)	0.545
YEARS negative	0 (0%)	3 (15%)	
YEARS not calculated	4	36	

Table 4: Pregnancy complications and comorbidities

Pregnancy complications	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
No complications	**0 (0%)**	**2 (3.6%)**	**>0,999**
Obstetric Haemorrhage	**5 (45,5%)**	**19 (33.9%)**	**0,505**
Ante-partum haemorrhage	2 (18.2%)	6 (10.7%)	0,609
Post-partum haemorrhage	3 (27.3%)	13 (23.2%)	0,7159
Hypertensive Disorders	**7 (63.6%)**	**42 (75%)**	**0,469**
Pregnancy induced hypertension	1 (9.1%)	12 (21.4%)	0,677
Pre-Eclampsia	3 (27.3%)	18 (32.1%)	>0,999
Eclampsia	1 (9.1%)	9 (16.1%)	>0,999
HELLP	2 (18.2%)	3 (5.4%)	0,186
Obstetric Complications	**4 (36.36%)**	**6 (10.71%)**	**0,051**
Placenta praevia	1 (9.1%)	2 (3.6%)	0,421
Preterm labour	0 (0%)	2 (3.6%)	>0,999
Other	**10 (90.1%)**	**42 (75%)**	**0,4329**
Post-partum cardiomyopathy	2 (18.2%)	13 (23.2%)	>0,999
Anaemia	8 (72.7%)	29 (51.8%)	0,321
Relook laparotomy	**3 (27.2%)**	**8 (14.3%)**	**0,371**
ICU	**5 (45.5%)**	**14 (25%)**	**0,27**
Comorbidities	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
Autoimmune disease	1 (9.1%)	3 (5.4%)	0.521
Anti-phospholipid syndrome	0 (0%)	2 (3.6%)	>0.999
Chronic kidney disease	0 (0%)	4 (7.1%)	>0.999
Diabetes mellitus	1 (9.1%)	1 (1.8%)	0.304
Heart failure	0 (0%)	8 (14.3%)	0.335
Hypertension	2 (18.2%)	9 (16.1%)	>0.999
Previous Tuberculosis	0 (0%)	2 (3.6%)	>0.999
Valvular heart disease	0 (0%)	5 (8.9%)	0.582
Previous VTE	0 (0%)	4 (7.1%)	>0.999
HIV	2 (18.2%)	17 (30.4%)	0.722

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APPENDIX A: ETHICAL CLEARANCE - HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Wilhelm Herbst

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M220255

NAME: (Principal Investigator)	Dr Wilhelm Herbst
DEPARTMENT:	Internal Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Review of the Use of CT Pulmonary Angiography in Pregnant and Postpartum Patients at an Academic Centre
DATE CONSIDERED:	25/02/2022
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr J. Zamparini, Dr H. Moodley and Dr S. Bhoora
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/05/2022

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

22/05/2022
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX B: ETHICAL CLEARANCE - CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA





CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL
UNIVERSITY OF THE WITWATERSRAND
Cluster Research Committee
7 Jubilee Rd, Parktown 2196, Johannesburg
Enquiries: Office of the CEO
Ms. T. Ndlovu; Tell: 011 488 4211 Fax 011 488 3753
Ms M. Khumalo Tel: 011 717 2536
Email: Mandisa.Khumalo@wits.ac.za

Dear Dr Wilhelm Herbst

The Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Research Cluster Committee has reviewed your request to research "A Review of the Use of CT Pulmonary Angiography in Pregnant and Postpartum Patient at an Academic Centre ".

I am pleased to inform you that you have been granted to research Charlotte Maxeke Johannesburg Academic Hospital provided that;

1. Charlotte Maxeke Johannesburg Academic Hospital will not anyway incur or inherit costs as result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

The data collection to be started only after obtaining the Human Research Ethics Committee (HREC) *unconditional approval*.

Kindly note that it is a requirement at CMJAH that for *unconditional approval* to be granted, all pending documents highlighted below are to be submitted as soon as they are available or within 3 months, and if not applicable, kindly elaborate. Failure to comply with the above-stated requirements may result in the withdrawal of this research's approval at CMJAH.

Head(s) of Department(s) Approval Letter	Provided
Human Research Ethics Committee Approval	Provided
The National Health Research Database Registration	Provided
Data Collection Sheets	Provided
Informed Consent Documents	N/A

Kindly forward this office with the results of your study on completion of the research.

I wish you every success with your research.

Yours sincerely,

Ms G. Bogoshi
Chief Executive Officer

7 Jubilee Rd, Parktown 2196, Johannesburg
Enquiries: Office of the CEO
Ms. T. Ndlovu; Tell: 011 488 4211 Fax 011 488 3753
Ms M. Khumalo Tel: 011 717 2536
Email: Mandisa.Khumalo@wits.ac.za

CMJA Hospital Research Checklist

Requirement	Yes	No	N/A
HOD Approval Letter	Yes		
HREC Approval	Yes		
NHRD Approval	Yes		
Postgraduate Approval	Yes - Pending		
Co-investigators	Yes		
Collaborators	Yes		

Study team and collaborators

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Collaborators			

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2.2 ABSTRACT

Background: Pulmonary embolism (PE), is a common cause of maternal death during pregnancy and the puerperium yet data on its prevalence in middle-income countries is lacking.

Methods: We examined the medical records and CTPAs of 67 women in an obstetric high care unit during pregnancy and the puerperium. We aimed to assess the efficacy of CTPA in diagnosing PE, evaluate associated clinical features, and determine the prevalence of alternative CT findings.

Results: CTPA detected PE in 11 women (16.42%) and alternative CT findings in 46 (68.6%). Women with PE had a significantly lower systolic BP than those without PE ($p = 0.001$). Multiple gestation, preterm rupture of membranes, and gestational diabetes were linked to higher PE prevalence.

Conclusions: This study, set in an upper middle-income country, demonstrated a higher CTPA yield for PE than in the international literature, emphasizing context-specific assessments.

2.3 INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE), is the most common cause of maternal death during pregnancy and the puerperium in developed countries.[1] The risk for venous thromboembolism (VTE) is significantly increased during pregnancy and the postpartum period, as these patients are in a physiological state of hypercoagulability, are prone to venous stasis and may have superimposed endothelial damage.[2]

Women have a 5-fold increased risk of developing VTE during pregnancy, as compared to their non-pregnant counterparts.[3] Globally, the incidence of PE in pregnant or postpartum women ranges from 1-2 per 1,000 to 3 per 10,000 deliveries [2,4], and one death in every 100,000 deliveries.[5] In South Africa PE accounted for 40 maternal deaths in 2022, with a maternal mortality rate of 4.1 per 100,000 live births.[6]

More than half of VTE cases in pregnancy occur before 20 weeks' gestation,[4] and 80% of VTE cases in the postpartum period occur within the first 3 weeks following delivery.[7]

Despite the increased risk of VTE in pregnancy, detection rates using CTPA (computed tomography pulmonary angiography) are lower in pregnant than non-pregnant women. A 2015 study found that 2% of pregnant women had a positive CTPA compared to 16% of non-pregnant women.[8] A 17-year retrospective study conducted at a single centre in Switzerland, published in 2020, observed that CTPA rarely indicated PE in pregnancy, with an alternative diagnosis found in 30% of pregnant women investigated.[9] Similarly, a 2023 study including 86 pregnant and 354 non-pregnant women investigated for PE by either CTPA or V/Q scan, noted positive scan rates of 3.5% and 8.8% in pregnant and non-pregnant women respectively.[10]

Risk Factors

Pregnancy is a hypercoagulable physiological state owing to an increased concentration of certain clotting factors as well as a decrease in endogenous anticoagulants such as antithrombin and protein S[11]. In addition, factors such as dehydration, secondary to nausea and vomiting in early pregnancy, immobility and iliac compression by the gravid uterus in late pregnancy, and endothelial injury from

delivery trauma and venous distension[11,12] also play a role in the increased risk for VTE. The clinical presentation of VTE may also be masked by "symptoms" of pregnancy such as pedal oedema, tachypnoea and tachycardia.[13] A number of postpartum factors are also associated with an increased risk of VTE, such as surgical delivery, particularly in the emergency setting or after prolonged labour, postpartum haemorrhage, thrombophilia, pre-eclampsia, and puerperal sepsis.[14]

Clinical predictors

The Wells' criteria, which factors in tachycardia and lower limb oedema, is not particularly useful in pregnancy, given that these manifestations are frequently seen.[15] This complicates the differentiation of PE from other potential diagnoses in these women.[15] The recommendations outlined by the Society of Obstetricians and Gynaecologists of Canada (SOGC)[16] and the Royal College of Obstetricians and Gynaecologists (RCOG)[17], advise against clinical predictors to assess VTE in pregnant women.

D-dimer

In non-pregnant women PE can be safely excluded in the presence of a normal D-dimer in addition to a low pre-test probability. It must conversely be interpreted with caution in those with a high pre-test probability, as a falsely negative result can miss a diagnosis of PE.[18] The American Thoracic Society (ATS)[19], SOGC[16], and RCOG[17] recommendations state that a D-dimer should not be used in pregnancy to exclude PE as most studies investigating the use of D-dimer in diagnosing PE, have not included pregnant women as participants.[20]

Van der Pol et al found that the pregnancy-adapted YEARS algorithm safely excluded acute PE in pregnant women with suspected PE, allowing CTPA to be avoided in 32 to 65% of women.[21] A South African study found that the pregnancy-adapted YEARS algorithm successfully risk-stratified women in a single institution and would have reduced the number of CTPAs by 25.7% without missing any PE.[22]

CT Pulmonary Angiography

Accepted standards outlined by the Royal College of Radiologists state that CTPA should detect PE in 15.4 - 37.4% and alternative diagnoses in up to 56% in the general population.[23]

Most studies have disregarded pregnant women when investigating the diagnosis of PE.[18] Certain physiological factors, such as increased circulatory volume and altered cardiac output, may lead to lower pulmonary artery opacification influencing the quality of CTPA.[24] Insufficient opacification of the pulmonary vasculature during CTPA is described twice as often among pregnant women compared to those who are not pregnant.[25] Normal CTPA imaging in pregnancy, has been found to have a high negative predictive value.[26]

In this study we investigated the use of CTPA to diagnose PE in pregnant and postpartum women admitted to a high care setting in South Africa. We aimed to evaluate the prevalence of PE and alternative diagnoses as well as compare the clinical features of women with and without PE.

2.4 METHODS

We performed a cross-sectional analysis at the Charlotte Maxeke Johannesburg Academic Hospital, an academic centre in Johannesburg, South Africa. Pregnant and postpartum women admitted to the Obstetric High Care Unit (OHCU) between 1 January and 31 December 2019, who underwent CTPA for the suspicion of PE were consecutively enrolled in this study. We excluded women who had a PE diagnosed by a method other than CTPA, such as V/Q scan, due to limited availability in our setting. Women with imaging performed elsewhere, women with known PE diagnosed prior to admission, and women who were not pregnant or beyond 6 weeks post-delivery were also excluded.

The names and hospital numbers of all women admitted to the OHCU for the study period were collected from the ward admission register and cross-referenced with the hospital picture archiving and communicating system (PACS) to determine which women underwent CTPA. The included participant details were anonymised and

allocated a unique study number. The CTPA images were reported on by two consultant radiologists (AR and TWT) who were blinded from each other's findings. The discrepant readings were reviewed by a third consultant radiologist (HM), also blinded from the findings of the other readers.

A final diagnosis was considered as agreement by two or more readers. Those studies with inconclusive findings or failing to achieve consensus among at least two readers, were interpreted as not having PE for the purposes of the study. The hospital files for the relevant participants were collected from hospital archives and clinical data was extracted. Data was captured in Microsoft Excel 16.78 (Microsoft Corporation, Redmond, USA) and statistical analysis was performed using Prism 10 (GraphPad Software Inc, La Jolla, CA, USA). Given the non-parametric nature of the data, the Mann-Whitney U test was employed for continuous variables, while the Fisher's exact test was utilized for categorical variables to determine significance.

2.5 RESULTS

A total of 732 women were admitted during the period under review, CTPAs were performed on 71 patients, of which 3 were not pregnant nor in the postpartum period and 1 had missing images, excluding them from the study, leaving a total of 67 women in the final analysis (Figure 1). The PE and non-PE groups were of similar age and race. The majority of the cohort were postpartum (82% in the PE group and 87.5% in the no PE group), and caesarean section was the most common mode of delivery in keeping with local trends. Most of the women were booked for antenatal care, and were multiparous. Table 1 provides demographic and pregnancy related data of the cohort.

Eleven women (16.4%) had a confirmed PE; 2 (18%) were pregnant and 9 (82%) postpartum and the majority (n=10, 90.9%) had peripheral PEs. Two women (18.2%) had a single embolism and 9 (81.8%) had multiple emboli.. The gestational age at delivery (in postpartum women) or time of scan (in pregnant women) was not significantly different ($p = 0.259$) in the non-PE group (median 34.5 weeks, IQR 30 – 38), compared to those with PE (median 30 weeks, IQR 26 – 38). Women with PE were more likely to have multiple gestation (27%) than without PE (4%) ($p = 0.028$).

There was a larger proportion of women with alternative CT findings among those in the group with PE (n=9, 81.8%) compared to those without PE (n=37, 66.1%), yet the difference was not significant (p=0.481) (Table 2).

The difference in the technical adequacy of the CTPAs between the two groups was not significant (p = 0.556). This was assessed by measuring the opacification of the pulmonary artery (Hounsfield units), between the two groups (median 237HU, IQR 216-277 versus median 247HU, IQR 209-285 in the PE and non-PE groups respectively). There was no difference in rate of motion artifact between the two groups (p = 0.492).

There was a significant difference in systolic blood pressure (sBP) between the two groups (p = 0.001) with lower sBP in the PE group (median 119mmHg, IQR 110 – 124) than in the non-PE group (median 134mmHg, IQR 120.3 - 146). There were no differences in other clinical features including the body mass index (BMI) or mid upper arm circumference (MUAC) between the two groups. Despite most women being tachycardic, there were no differences in electrocardiogram (ECG) findings between the two groups. It is not our standard protocol to analyse D-dimer routinely for the suspicion of PE in pregnancy, therefore only 27 women (40%) had D-dimers available. There was however no difference in D-dimers between the two groups (p = 0.219).

Biochemical inflammatory markers were available in a similar proportion of women, showing no difference between the groups, reflected by a median C-reactive protein (CRP) of 112mg/L in the PE group (10/11) and 100mg/L in the non-PE group (51/56) and a median procalcitonin (PCT) of 0.37ug/L in the PE group (8/11) and 0.31ug/L in the non-PE group. A diagnosis of puerperal sepsis was made in 36.4% in the PE group compared to 62.5% in the non-PE group, however the difference was not significant (p = 0.18). There were no other differences demonstrated in biochemistry between the two groups.

No women died in the non-PE group, while one woman died in the PE group (9%), however it is unclear if the death was directly caused by PE. Most women had a pregnancy-related complication, with the exception of 2 women (3.6%) in the non-PE group.

There were 2 women with HIV (18.2%) in the PE group, one of whom had a CD4 (CD4 = 464 cells/mm^3) and HIV viral load (VL = 764 copies/ml) available, whilst there were 17 women with HIV in the non-PE group (30.4%) where 15 had a CD4 result (median 344.5 cells/mm^3, IQR 269-457.75) and all had a viral load (n = 17, median 217 copies/ml, IQR 0 – 2472.25).

Gestational diabetes was significantly more prevalent (p = 0.042) among those with PE (n = 1, 9.1%) compared to those without PE (n = 2, 3.6%), as was premature rupture of membranes (PROM) (p = 0.025) comparing the PE group (n = 2, 18.2%) to the non-PE group (n = 0, 0%). There were no other complications or comorbidities with a significant difference between the groups (Table 3).

The Wells' score showed no correlation to PE, as all 67 (100%) women had a Wells' score of at least 4.5 (high risk for PE). When analysing the utility of the YEARS score [27], 7 women in the PE group and 20 women in the non-PE group had a D-dimer result available allowing the YEARS Score to be calculated. All 7 (100%) women in the PE group had a positive YEARS score, while 17 (85%) women in the non-PE group had a positive YEARS score. The difference was not significant (p = 0.545) (Figure 2).

2.6 DISCUSSION

In our study CTPA detected PE in 16.42% and alternative CT findings in 68.6% of our cohort, which is higher than reported in international literature. A large meta-analysis and systematic review of seventeen studies, including 25,339 women, found a 12.4% positivity rate for VTE in nonpregnant women, compared with 4.1% in pregnant women.[28] The high positivity rate in our cohort may be attributed to only including women admitted to a high care unit, assigning them to a higher risk category than other pregnant and postpartum women.

No clinical or biochemical biomarkers predicted PE in our cohort, similar to an Australian study evaluating the use of CTPA and V/Q in pregnancy and the puerperium.[29] The use of algorithms such as the modified YEARS and Wells' scores were limited in our cohort and would have been of no utility in reducing the number of

CT scans done. However given our limited sample size, future studies are needed to further assess their utility in our setting. This is in keeping with recommendations from RCOG to avoid the use of clinical prediction tools in assessing VTE in pregnancy.[17]

Despite international guidelines considering maternal age over 35 years a risk factor for PE there was no significant difference in the age of the PE and the non-PE groups in our cohort.[30] There is evidence from the UK[31] and USA[32] that Black, Asian and minority ethnicities (BAME) have a much higher maternal mortality rate (MMR), with the highest among Black women. There is evidence that PE is more prevalent in black ethnicities,[33] with a higher disease severity compared to other ethnicities.[34] The majority of our cohort were of Black ethnicity, making it difficult to compare outcomes related to ethnicity and to assess whether disparities exist.. This emphasises the importance of the high risk in this group, and the need for further research in a South African context

Caesarean delivery rate in the South African private sector was 73.2% in 2015[35], and increased from 15.1% in 2006[36] to 31.1% in 2022[6] in the public sector. Caesarean delivery is not done on maternal request in the South African public sector. Compared to the UK, the rate of caesarean delivery was 29%[31] in Wales, 31%[31] in England and 35%[31] in Scotland between 2019 - 2021. South African data shows that pregnant women who die from PE are more likely to have had a caesarean delivery.[37] In our cohort all women in the PE group were delivered by caesarean section, although this was for obstetric indications and not due to PE. While Caesarean delivery is a known risk factor for the development of PE[38], this was not demonstrated in our cohort and mode of delivery was not a risk factor for PE.

The most significant obstetric complication in our cohort was PROM with a higher prevalence in those with PE (n = 2, 18.2%) compared to those without PE (n = 0, 0%) (p = 0.025). Both women with PROM in the PE group were HIV positive, developed puerperal sepsis and had undergone caesarean delivery by gestational age of 28 and 35 weeks respectively. Only one of these women had a CD4 (CD4 = 464 cells/mm^3) and HIV viral load (VL = 764 copies/ml) available, and neither had a history of previous tuberculosis. PE was diagnosed after delivery in both women. The development of PE in these women was likely multifactorial however prolonged bed rest prescribed for the

treatment of PROM was associated with an increased risk for PE in a study by *Kovacevich et al* (16.5 cases per 1000 compared to 0.8 per 1000 among pregnant women for whom this therapy was not prescribed).[39]

Systolic BP was significantly lower ($p = 0.001$) in the PE group, as was seen in the DiPEP study, however there were no differences in diastolic BP and heart rate. Out of keeping with the lower systolic BP in the PE group is that majority of these were peripheral PEs. However 81.8% of the women with PE had multiple emboli which may have contributed to the lower systolic BP. Hypotension associated with PE is attributed to acute right ventricular dilatation compromising left ventricular filling and reducing cardiac output. Right ventricular dysfunction seen on echocardiography has been shown to correlate with pulmonary arterial obstruction of >30%, which is expected to occur with a large central PE[40]. Echocardiography was not available to assess for right ventricular strain, however there were no ECG features to suggest this.

The high prevalence of alternative findings on CTPA may be explained by the hospital's protocol for investigating PE, where CTPA is warranted if the chest X-ray is abnormal. Despite there being no significant difference in prevalence of alternative CT findings between women with PE and women without PE, the high burden of alternative findings on CTPA in women with PE could signify underlying pathology contributing to development of PE. The high prevalence of pregnancy related complications in our cohort is due to it consisting only of women in a high care setting.

Multiple gestation was a risk factor for PE in our cohort ($p = 0.028$) in keeping with guidelines from RCOG[17]. Gestational diabetes has not been proven to be associated with an increased risk for thrombosis[41], however was associated with PE in our cohort ($p = 0.042$). Despite HIV[42], antiphospholipid syndrome[43], and obesity[44] known to be associated with increased risk for PE, none were significant risk factors in our cohort.

The strengths of this analysis are driven from the racial representation in our cohort, largely consisting of Black African women, an underrepresented group in other studies, which underpins the need and potential for further research. Additionally, the data investigated were largely complete, all the CTPAs in our cohort contained adequate quality images, and were reviewed by consultant radiologists. Yet, the findings of this

analysis must be interpreted in the context of some limitations. The first being, the small sample size. Considering our study was performed at a single centre including only women admitted to a high care setting, this in itself might be a major contributory factor to the high PE burden in our population, as these women were all in a higher risk category by nature of their condition. Another limitation is that chest radiographs were not reviewed, as this could have contributed to analysing the pre-test probability for PE.

2.7 CONCLUSION

PE remains a significant contributor to morbidity during pregnancy and the puerperium. While clinical and laboratory features were not reliable to exclude PE in our cohort, it is justifiable to consider CTPA when suspecting PE in this population, considering the higher detection rate compared to international literature. CTPA has a good yield for diagnosing PE and unmasking alternative diagnoses in a middle-income country setting. The presence of a low systolic blood pressure, multiple gestation, PROM, and gestational diabetes should raise the suspicion for PE in a high care setting. Prospective studies evaluating the use of d-dimer and scoring systems to predict PE in our population are warranted.

2.8 TABLES AND FIGURES:

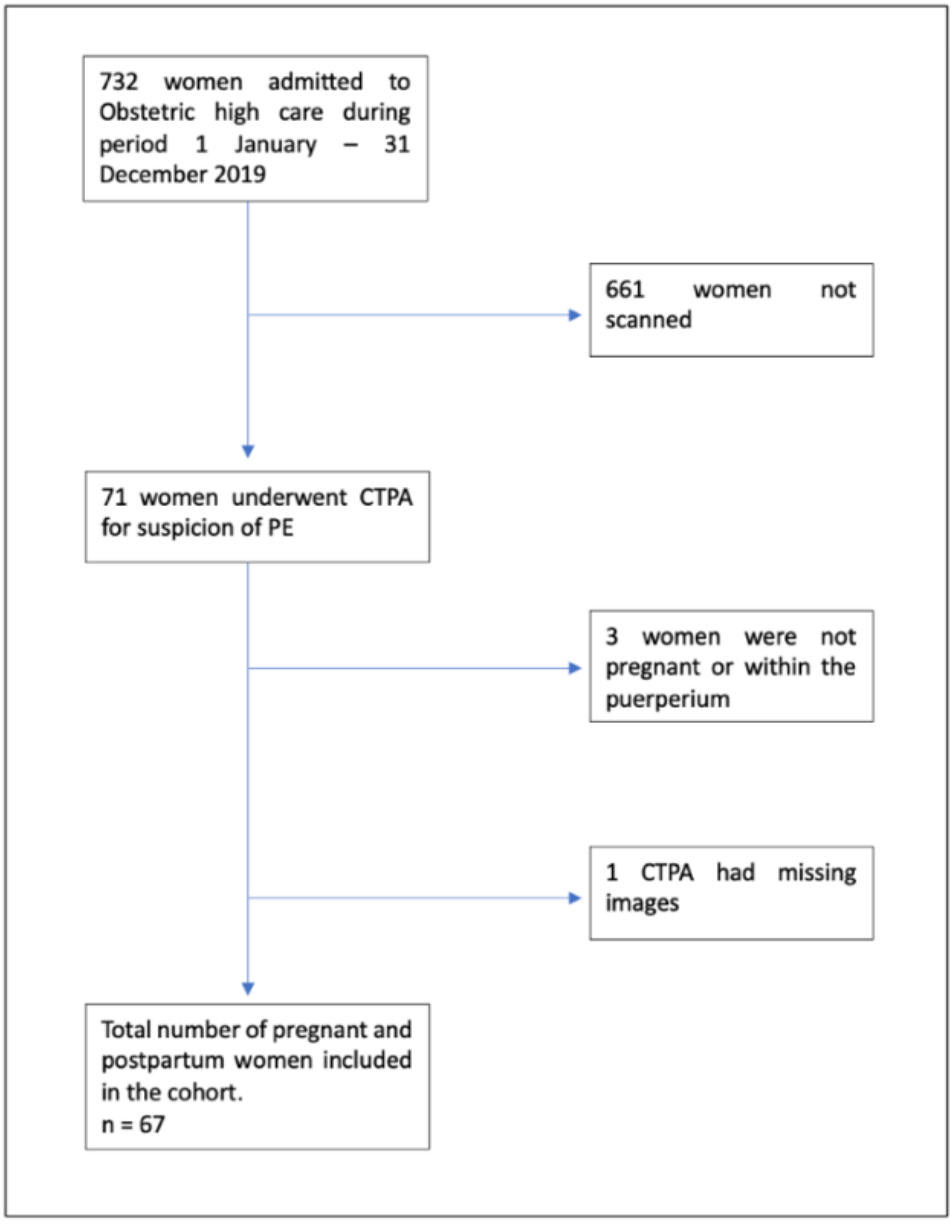

Figure 1: Study population

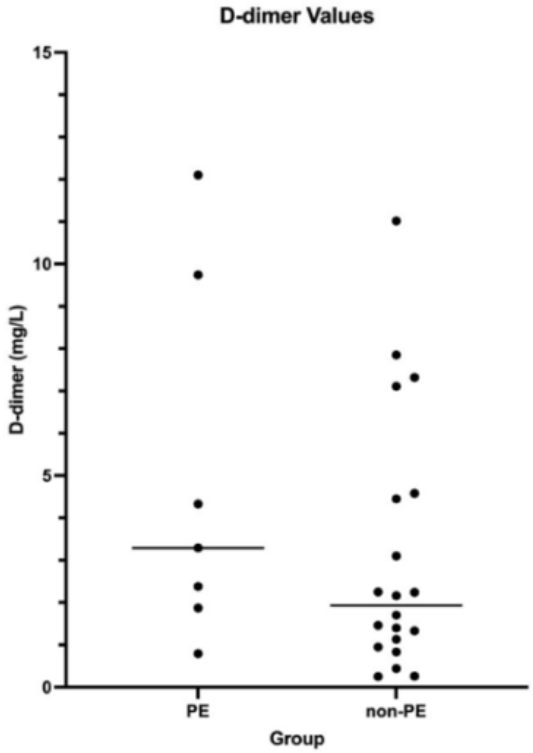

Figure 2: D-dimer values

Table 1: Demographics and pregnancy details

Demographics	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
Age (years), median, (IQR)	29 (26 – 35)	30 (26 – 33,75)	0.977
18 – 25	2 (18.18%)	12 (21.43%)	0.992
26 - 30	4 (36.36%)	18 (32.14%)	
31 - 35	3 (27.27%)	16 (28.57%)	
>35	2 (18.18%)	10 (17.86%)	
Race	PE, n (%)	No PE, n (%)	p-value
Black African	11 (100%)	55 (98%)	>0.999
White	0 (0%)	1 (2%)	
Pregnancy Details	PE, n (%)	No PE, n (%)	p-value
Postpartum	9 (82%)	49 (87.5%)	0.635
Pregnant	2 (18%)	7 (12.5%)	
Multiple gestation	3 (27%)	2 (4%)	0.028
Booked for antenatal care	8 (73%)	45 (80%)	0.686
Not booked for antenatal care	3 (27%)	11 (20%)	
Gestational age at delivery or time of scan (weeks), median (IQR)	30 (26 – 38)	34,5 (30 – 38)	0.259
Caesarean section	9 (82%)	41 (73.2%)	0.334
Normal vaginal delivery	0 (0%)	8 (14.3%)	
Gravidity (number of pregnancies), median (IQR)	3 (1 – 3)	2 (1 – 3)	0.971
Parity (number of live births) , median (IQR)	2 (1 -3)	2 (1 – 3)	0.714
Previous miscarriages (number), median (IQR)	0 (0 – 0)	0 (0 – 0)	0.841

Table 2: Alternative CT findings

CT findings	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
Pleural effusion	4 (36.4%)	14 (25%)	0.469
Ground glass opacification	6 (54.5%)	16 (28.6%)	0.157
Consolidation	3 (27.3%)	11 (19.6%)	0.686
Cavitation	0 (0%)	1 (1.8%)	>0.999
Bronchiectasis	0 (0%)	2 (3.6%)	>0.999
Atelectasis	8 (72.7%)	24 (42.9%)	0.101
Nodules	0 (0%)	5 (8.9%)	0.582

Table 3 YEARS score

YEARS score	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
YEARS positive	7 (100%)	17 (85%)	0.545
YEARS negative	0 (0%)	3 (15%)	
YEARS not calculated	4	36	

Table 4: Pregnancy complications and comorbidities

Pregnancy complications	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
No complications	**0 (0%)**	**2 (3.6%)**	**>0,999**
Obstetric Haemorrhage	**5 (45,5%)**	**19 (33.9%)**	**0,505**
Ante-partum haemorrhage	2 (18.2%)	6 (10.7%)	0,609
Post-partum haemorrhage	3 (27.3%)	13 (23.2%)	0,7159
Hypertensive Disorders	**7 (63.6%)**	**42 (75%)**	**0,469**
Pregnancy induced hypertension	1 (9.1%)	12 (21.4%)	0,677
Pre-Eclampsia	3 (27.3%)	18 (32.1%)	>0,999
Eclampsia	1 (9.1%)	9 (16.1%)	>0,999
HELLP	2 (18.2%)	3 (5.4%)	0,186
Obstetric Complications	**4 (36.36%)**	**6 (10.71%)**	**0,051**
Placenta praevia	1 (9.1%)	2 (3.6%)	0,421
Preterm labour	0 (0%)	2 (3.6%)	>0,999
Other	**10 (90.1%)**	**42 (75%)**	**0,4329**
Post-partum cardiomyopathy	2 (18.2%)	13 (23.2%)	>0,999
Anaemia	8 (72.7%)	29 (51.8%)	0,321
Relook laparotomy	**3 (27.2%)**	**8 (14.3%)**	**0,371**
ICU	**5 (45.5%)**	**14 (25%)**	**0,27**
Comorbidities	PE (n = 11), n (%)	No PE (n = 56), n (%)	p-value
Autoimmune disease	1 (9.1%)	3 (5.4%)	0.521
Anti-phospholipid syndrome	0 (0%)	2 (3.6%)	>0.999
Chronic kidney disease	0 (0%)	4 (7.1%)	>0.999
Diabetes mellitus	1 (9.1%)	1 (1.8%)	0.304
Heart failure	0 (0%)	8 (14.3%)	0.335
Hypertension	2 (18.2%)	9 (16.1%)	>0.999
Previous Tuberculosis	0 (0%)	2 (3.6%)	>0.999
Valvular heart disease	0 (0%)	5 (8.9%)	0.582
Previous VTE	0 (0%)	4 (7.1%)	>0.999
HIV	2 (18.2%)	17 (30.4%)	0.722

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