Clinical predictors of pulmonary embolism in pregnancy and immediate postpartum period: a retrospective, analytical study

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DECLARATION

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ABSTRACT

Background

Although pulmonary embolism (PE) is one of the leading causes of death in pregnancy and postpartum, it has low risk of adverse outcome if diagnosed early and treated appropriately. Ventilation-perfusion scanning (VQ scan) or computed tomography pulmonary angiogram (CTPA) are widely used to confirm or diagnose PE, however it carries risks to the mother and the fetus.

Up to date, there is no validated clinical predicting tool that can be used in pregnancy and postpartum, thus clinicians face a challenge when suspecting PE in pregnancy and postpartum. Furthermore, the lack of medical resources in low resource environments contributes to the delay of investigations and diagnosis of PE.

This study aimed to describe clinical markers for suspicious PE amongst pregnant mothers and immediate postpartum and to design a practical, clinical tool for accurate diagnosis of PE peripartum in our population.

Methods

The study was performed as a retrospective and analytical study over a period of four months, in the Obstetric Unit at Tygerberg Academic Hospital.

The files (total 100) of the patients who were suspected of having PE and underwent imaging (VQ scan or CTPA) were retrospectively evaluated (ECM) to see if there was an association between clinical presentation and PE. All obstetric patients who were imaged for suspected PE, antenatal and immediate postpartum admitted to F2, C2A, OCCU, J2, J4 and J5 were included but not any patients already known with PE or varicose thrombosis.

Results

There was a statistically significant (P <0.05) association between PE occurrence and ten assessed factors (surgery in <4/52, immobilization >3/7, SOB, hemoptysis, sudden onset of pleuritic chest pain, respiratory alkalosis, sinus tachycardia, deep S1, Q3/T3 and HIV).

Conclusion

The researcher designed a clinical PE predicting tool that may be used in pregnancy and postpartum.

Keywords

Pulmonary embolism, antenatal, immediate postpartum

LIST OF ABBREVIATIONS

PE	Pulmonary Embolism
TBH	Tygerberg Academic Hospital
PT	Patient
DVT	Deep vein Thrombosis
BMI	Body Mass Index
HIV	Human Immune Deficiency Virus
ABG	Arterial Blood Gas
MWS	Modified Wells Score
SOB	Short of Breath

1 CONTENTS

Clinical predictors of pulmonary embolism in pregnancy and immediate postpartum period: a retrospective, analytical study

1 INTRODUCTION AND MOTIVATION

Pulmonary embolism (PE) is a life-threatening, sudden occlusion of a lung artery as a result of a blood clot that was dislodged from any other part of the body, usually the legs (Armstrong et al 2017). It is one of the leading causes of mortality in pregnancy and immediate post-partum in the world. No clinical prediction models have been validated yet in pregnancy. Thus, any pregnant woman presenting with signs possibly consistent with pulmonary embolism is investigated radiologically.

According to Van de Pol (2017), the increased level of estrogen and clotting factors (V, VIII, IX, X and fibrinogen) during pregnancy, venous stasis due to fetal compression of pelvic veins in pregnancy, reduced protein S and reduced fibrinolysis in pregnancy. Pulmonary embolism has been found to be five-fold higher in pregnancy (Cutts et al 2013). Normal physiological changes in pregnancy such as chest pain and dyspnea make it difficult to diagnose pulmonary embolism.

D-dimers also rise gradually throughout pregnancy and normal cutoff values for D-dimer assays have not been validated in pregnancy. Keeping this in mind, the diagnosis of pulmonary embolism in pregnancy is usually based on computed tomography pulmonary angiography (CTPA) and ventilation perfusion scanning (VQ scans). However, according to WS Chan (2018), the rates of high-probability VQ scans are much lower in pregnancy than in the non-pregnant population (<5% versus 20%), and due to suboptimal imaging from altered contrast dynamics from increased cardiac outputs in pregnancy, CTPA can be nondiagnostic in up to 20% of pregnant patients. During gestation, both modalities expose the fetus to radiation and CTPA confers an increased risk of breast cancer (Cutts et al 2013.) Hence, a system that stratifies pregnant women as low risk for pulmonary embolism and hence avoids unnecessary imaging would be ideal.

The modified Wells score (MWS) is a simpler stratification system for suspected PE. Patients with a score of 4 or less are being classified as 'pulmonary embolism unlikely' and a score of more than 4 as 'pulmonary embolism likely' (Cutts et al 2013). In the Christopher study it was described (Van Belle et al 2006) that the MWS had a high negative predictive value when combined with negative D-dimers (>99%) for prediction of pulmonary embolism in the non-pregnant population. But it has never been prospectively validated in pregnancy (Briony et al 2014).

Goldhaber (2012), states that clinical predictors, such as Body Mass Index, complications of pregnancy, previous venous thromboembolism, peripheral oxygen saturation and modified Wells score, may be used to identify women at higher risk of PE for imaging, but none had been sufficiently validated to support a recommendation for clinical use.

Pulmonary embolism (PE) is one of the leading causes of death in pregnancy and postpartum, but women who are appropriately diagnosed and treated for PE have a low risk of adverse outcome. Furthermore, the outcome for the fetus depends on the outcome for the mother. However, the investigations used to diagnose PE (VQ scanning or CTPA) carry risks of radiation exposure, reaction to contrast media and false positive diagnosis and can cause unnecessary psychological distress to the patients.

MRI has the potential to avoid ionizing radiation exposure, but there is insufficient evidence to support inclusion in guidelines. Therefore, clinicians face a challenge when deciding whether to use diagnostic imaging to investigate patients for suspected PE in pregnancy and postpartum and between risking potentially catastrophic consequences of missed diagnosis if imaging is withheld and risking iatrogenic harm if imaging is overused (Armstrong et al 2017).

Therefore, the main objectives of this study were to evaluate performance of the symptoms system that can be utilized in our environment and other settings and to evaluate the requested images done for suspicious PE in pregnant and immediate postpartum mothers in Tygerberg Academic Hospital (TBH) and possibly design a scoring tool.

Having a clinical PE scoring tool will be of a benefit in our current environment of limited resources with inadequate and unavailability of imaging. It would be a great achievement if clinical predictors of PE in pregnancy and immediate postpartum period can be determined and used as a diagnostic tool of PE. This would save a lot of lives as those who will be graded as most likely PE can be initiated on therapeutic anticoagulant soon after referral and prior to imaging. Secondary, it will be cost effective and prevent unnecessary exposure. That puts them at increased chance of breast cancer and have a negative effect to the unborn fetus. Furthermore, our study aimed to describe clinical markers for suspicious PE amongst pregnant mothers and immediate postpartum and to design a practical clinical tool for accurate diagnosis of PE peripartum in our population.

2 METHODOLOGY

The study was performed as a retrospective and analytical study over a period of four months, in the Obstetric Unit at TBH, a secondary and tertiary referral center. The research described all the images done for suspicious PE in pregnant and immediate postpartum mothers.

The files (total 100) of patients who were suspected of having PE and underwent imaging (VQ scan or CTPA) were retrospectively evaluated (ECM) by looking at the clinical picture they presented with. The files were categorized into two groups, those who were diagnosed PE positive and PE negative. The study was approved by the Stellenbosch University Health Research Ethics Committee (HREC). **Project ID: 11708, S/9/10/205.**

2.1 Inclusion

All obstetric patients who were imaged for suspected PE, labour ward, antenatal and immediate postpartum (5 days) admitted to F2, C2A, OCCU, J2, J4 and J5 (antenatal and postpartum wards). Study sample was 100 patients.

Certain factors were identified at and their implications on an individual in developing PE (see the appendix for parameters). Request for VQ or CTPA.

2.2 Exclusion

All non-obstetric patients, patients already known with PE or varicose thrombosis (See abstract).

2.3 Statistical Analysis

Descriptive statistics were used. The data was captured in Excel and the statistical analysis was performed using standard techniques with the help of a biostatistician. For continuous variables means with standard deviations were calculated for normal distribution data, and medians, with ranges and interquartile ranges, were calculated for skewed data. Categorical data was presented as frequencies and percentages, and the chi-squired test and the Fisher's exact test at a significance level of P=0.05 was used to test for any association between the variables. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio were computed from the following formulas:

$$Sensitivity = \frac{True\ Positive}{True\ positives + Fals\quad Negative} \qquad \text{Eq1}$$

$$Spesitivity = \frac{True\ Negatives}{True\ Negatives + Fa\quad\ Positives} \qquad \text{Eq2}$$

$$LR+= \frac{Sensitivity}{1-Specificity} \qquad \text{Eq3}$$

$$LR-= \frac{1-Sensitivity}{Specificity} \qquad \text{Eq4}$$

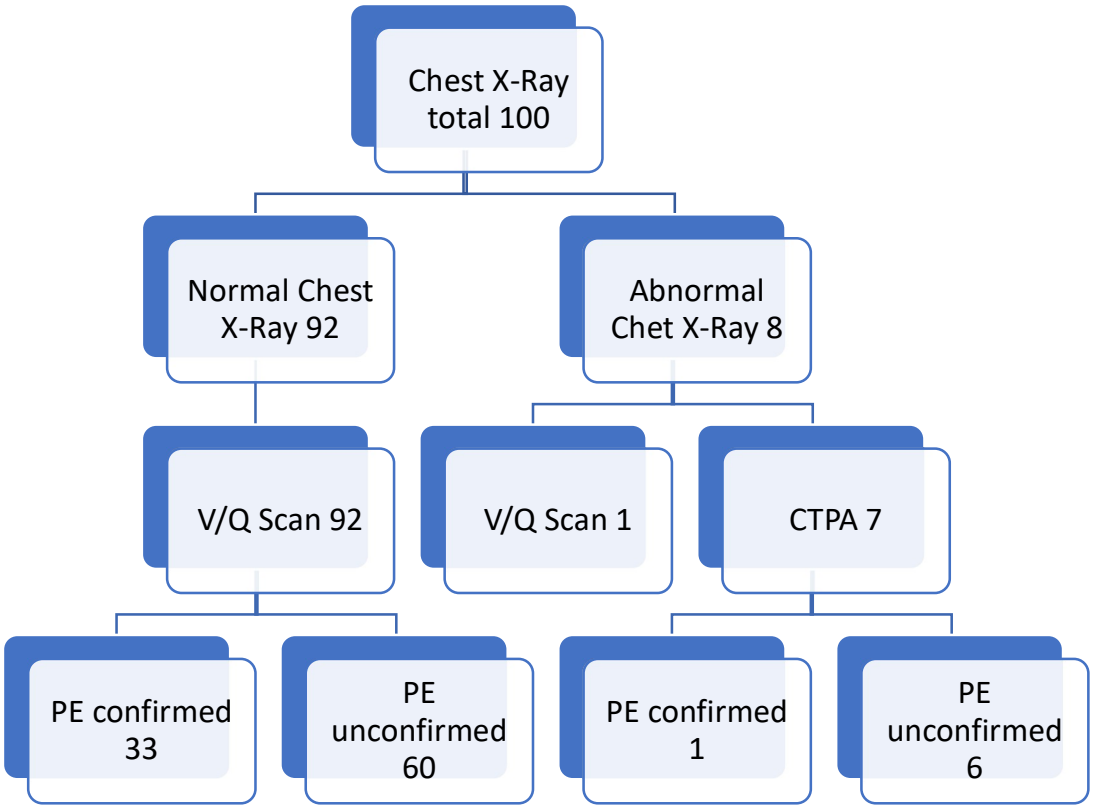
3 RESULTS

Table 1: The distribution of VQ and CTPA scans across 100 women

Diagnostic tests	**Amount**
Computed tomography pulmonary angiogram (CTPA)	7
Ventilation-perfusion scan (VQ scan)	93
TOTAL	**100**

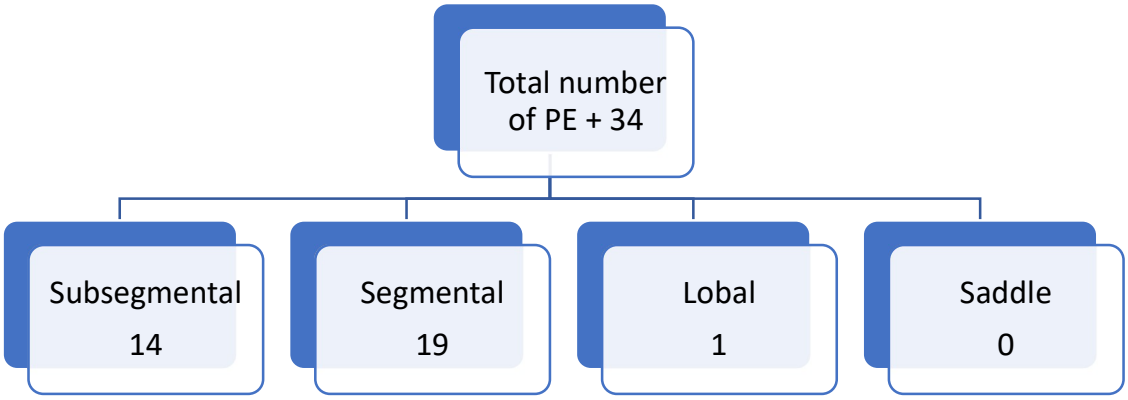
Above table shows an overall, 100 conveniently sampled and de-identified hospital files that met the study criteria were included. As per hospital protocol, all de-identified patients had a chest X-ray done prior to PE diagnostic imaging. Depending on the chest X-ray report, patients had either VQ or CTPA done as a diagnostic image. The inclusion period of the study was four months, retrospectively from September to December 2019. The Pearson's chi-square test was used to assess the association between the occurrence of PE and the patient-related considered factors. A summary of the results are shown in Tables 1-3 and Figures 1-3.

Figure 1: Distribution of patients who were confirmed with pulmonary embolism (PE)+ among patients who underwent VQ scan and CTPA



As shown above, all de-identified patients (100) had a chest X-ray done prior to PE diagnostic imaging. A total of 92 women had normal chest X-rays and eight (8) had abnormal chest X-rays. As per hospital protocol, VQ scan as a diagnostic method was performed to those who had normal chest X-ray and CTPA to those who had abnormal chest Xray. However, for unknown reason, VQ scan was performed on one patient who had an abnormal chest X-ray (Figure 1). Thirty-three patients (33) who had VQ scans were confirmed to have PE positive and only one (1) patient amongst those who had CTPA, was confirmed with PE positive. A total of 34 patients (34%) were confirmed PE positive radiologically.

Figure 2. Distribution of types of pulmonary embolism detected based on the location



Amongst 34 patients who were confirmed with pulmonary embolism, predominantly, patients had segmental pulmonary embolism (55.8%) followed by subsegmental type (41%). Only one (1) patient had lobal type of PE, while saddle type of PE was not detected.

Table 2: Characteristics of pregnant and postpartum (<1 week) women underwent CTPA and VQ scan to detect the occurrence of pulmonary embolisms.

2.1 Patient's profile and clinical history					
Predictors	**Characteristics**	**PE (+) n=34**	**PE (-) n=66**	**TOTALS (n)**	**p-**
Age					
<34 years old		27 (32.93)	55 (67.07)	82	0.629[1]
≥34 years old		7(38.89)	11 (61.11)	18	
BMI	<29.9	12 (40.00)	18 (60.00)	30	0.708[1]
	30.0-39.9	9(31.03)	20(68.97)	29	
	>40	13 (31.70)	28 (68.30)	41	
HIV	Positive	9(60.00)	6(40.00)	15	**0.021[1]**
	Negative	25(29.41)	60(70.59)	85	
Multiparity	Parous	19 (35.19)	35 (64.81)	54	0.786[1]
	Non-parous	15 (32.61)	31 (67.39)	46	
EGA on requisition date	Antenatal	10 (26.32)	28 (73.68)	38	0.204[1]
	Postnatal	24 (38.71)	38 (61.29)	62	
History					
Previous DVT/PE	YES	1 (0.50)	1 (0.50)	2	0.629[2]
	NO	33 (33.67)	65 (66.33)	98	
Surgery <4 weeks	YES	18 (47.37)	20 (52.63)	38	**0.027[1]**
	NO	16 (25.81)	46 (74.19)	62	
Immobilized >3 days	YES	17 (48.57)	18 (51.43)	35	**0.024[1]**
	NO	17 (26.15)	48 (73.85)	65	

[1]Pearson's chi-square (2- sided), [2]Fisher's exact test (1- sided)

2.2 Signs and Symptoms of DVT					
Predictors	**Characteristics**	**PE (+) n=34**	**PE (-) n=65**	**TOTALS (n)**	**p-**
Calf pain and tenderness	YES NO	0 (0.00) 34 (34.69)	2 (100.00) 64 (65.31)	2 98	0.547[2]
Unexplained unilateral leg swelling	YES NO	0 (0.00) 34 (34.69)	2 (100.00) 64 (65.31)	2 98	0.433[2]
Tachycardia	YES NO	34 (34.34) 0 (0.00)	65 (65.66) 1 (100.00)	99 1	0.660[2]
SOB	YES NO	28 (82.35) 6(9.09)	6 (17.65) 60 (90.91)	34 66	**0.000[2]**
Unexplained sweating	YES NO	2 (28.57) 32 (34.41)	5 (71.43) 61 (65.59)	7 93	0.555[2]
Haemoptysis	YES NO	10 (66.67) 24 (28.24)	5 (33.33) 61 (71.76)	15 85	**0.006[2]**
Sudden onset pleuritic chest pain	YES NO	24 (82.76) 10 (14.08)	5 (17.24) 61 (85.92)	29 71	**0.000[2]**
Malignancy	YES NO	0 (0.00) 34 (34.00)	0 (0.00) 66 (66.00)	0 100	-

[1]Pearson's chi-square (2- sided), [2]Fisher's exact test (1- sided)

2.3 Special investigations					
Predictors	**Characteristics**	**PE (+) n=34**	**PE (-) n=65**	**TOTALS (n)**	**P value**
ABG respiratory alkalosis	YES NO	7(0.88) 23(0.31)	1(0.12) 52(0.69)	8 75	**0.0001[1]**
Electrocardigram					
Sinus tachycardia (>120bpm)	YES NO	32 (43.24) 2 (7.69)	42 (56.76) 24 (92.31)	74 26	**0.0001[1]**
Deep S-wave in I	YES NO	23 (74.19) 11 (16.18)	9 (25.81) 57 (83.82)	32 68	**0.0001[1]**
Deep T-wave in III	YES NO	30 (73.17) 4 (6.90)	11 (26.83) 54 (93.10)	4 58	**0.0001[2]**
Deep Q-wave in III	YES NO	29 (69.05) 5 (8.62)	13 (30.95) 53 (91.38)	42 58	**0.0001[1]**

[1]Pearson's chi-square (2- sided), [2]Fisher's exact test (1- sided)

As shown in Table 2, there was a statistically significant (P <0.05) association between PE occurrence and ten assessed factors **(surgery in <4/52, immobilization >3/7, SOB, hemoptysis, sudden onset of pleuritic chest pain, respiratory alkalosis, sinus tachycardia, deep S1, Q3/T3 and HIV).**

There was strong statistical significance between PE and hemoptysis (P 0.006[2]) as well as respiratory alkalosis (P 0.001[1]) and sinus tachycardia (P 0.001[2]), while SOB (P 0.000[2]), pleuritic chest pain (P 0.000[2]), S1 (P 0.000[1]) and Q3/T3 (P <0.000) were found to be statistically highly associated with PE.

The study found no association between age groups (P 0.629[1]), calf pain (P 0.547[2]), unexplained unilateral leg swelling (P 0.433), unexplained sweating (P 0.555-2), BMI (P 0.708[1]) and parity (P 0.786[1]). Surprisingly, there were also no statistical difference in the association with PE between antenatal and postnatal women (P 0.204[1]) as well as in women who previously had PE/DVT (P 0.629[2]).

There was no-one woman with malignant disease (active or in history) hence calculation of statistically difference or association was impossible. The study found no statistical association between PE and vital signs (Bp, pulse, respiration) whether below or above the normal limit (P >0.337[1]).

Table 3. Association between the scores and actual outcome results

Score	Sum of patients	PE negative	PE positive
0 – 5	62	62 (100%)	0
6 and above	38	4 (10.52%)	34 (89.47%)

The above table depicts the sum of investigated patients who scored 0 to 5 and 6 or above. It signifies that patients with score of 6 and above, only 10.52% had no PE and majority were PE positive. While none of the patients was confirmed with PE amongst those with score of 5 and less.

Table 4. Pulmonary embolism clinical predicting tool (scoring system)

Predictors	**Score per predictor (circle if present)**	**0 score if absent**
1. Surgery < 4 weeks	1	
2. Immobilization for > 3 days	1	
3. Short of breath	3	
4. Haemoptysis	2	
5. Pleuritic chest pain	3	
6. Respiratory alkalosis	2	
7. Tachycardia	2	
8. ECG : Sinus tachycardia	1	
9. ECG: S1/T3/Q3 • S1 (deep S wave in lead I)	1	
• Q3 (prolonged Q in lead III)	1	
• T3 (inverted T in lead III)	1	
10. HIV	1	
PATIENT'S TOTAL SCORE		
PE most likely (6 or more)		
PE less likely (5 or less)		

Above table 4 shows the 10 clinical predictors of PE identified in this study, **the scoring predicting tool system of PE.** A clinical PE predicting tool has been designed using a points system. Point/s were allocated to each statistically significant predictor (See predicting tool, table 4). Strong association for confirmed PE was found between the patients with score of 6 and more and no association with the score of 5 and less (See Figure 3).

Thus, a scores of 0-5 were classified as PE less likely, hence no further investigations needed and a score of 6 or more were classified as PE most likely and immediate treatment with LMWH need be initiated. This tool should be investigated in a larger, prospective study to validate its effectiveness.

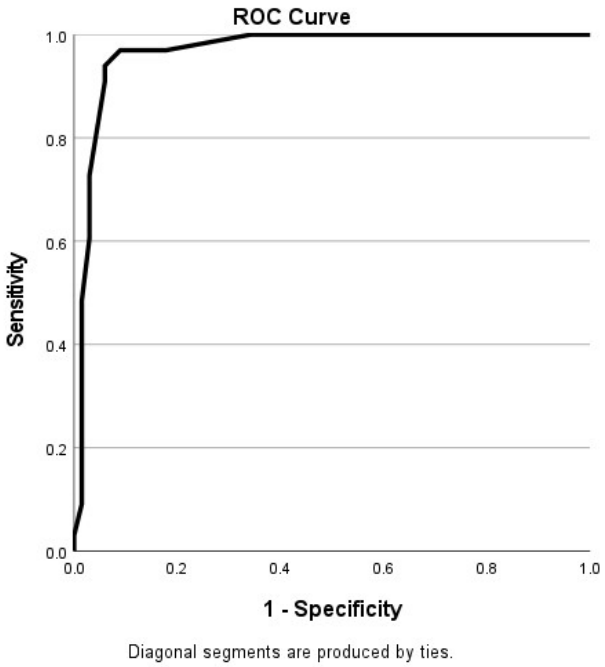
3.1 Receiver Operating Characteristic (ROC) curve

Graph (Figure 3) with a point at which we maximize the true positive rate (sensitivity) and true negative identification rate (False positive rate=1-specificity).

Sensitivity = true full positive totals

Spec = True negative test results

Figure 3: Receiver Operating Characteristic (ROC) Curve predicting the presence or absence of Pulmonary Embolism (PE) in pregnant and postpartum (≤1 week) women (with the score of ≤5 representing women without PE and while score of ≥6 represent women with PE +).



As shown above on the ROC curve, the area under the curve is high and very close to the Y-axis and to 1.0. This predicts that, a score of six and above is a good test for prediction of PE clinically.

In order to conduct the ROC curve a demarcation point was required based on the above points scale, which would be used to differentiate between predicting PE+ and PE- women.

We have two measures: the **actual result** i.e., women shown to have PE (PE+) and women who do not have PE (PE-) and the **scoring system** (Table 4) which is an accumulation of weighted scoring across statistically significant predictors from our study.

The actual results are our criterion variable, which together with the predictor points scale assist in finding the demarcation (in the ROC curve). The positive likelihood ratio from the calculated sensitivity and specificity ranged from 1 to 32.33 with an average of 12.488 ± 9.868 while the negative likelihood ratio ranged from -12.33 to 1.000 with an average of -0.653 ± 3.298 (Table 5). Higher than 10 positive likelihoods significantly increase the probability of positive PE while lesser than 1 negative likelihood ratio decreases the probability of patients having PE. Therefore, the results imply that on average, there was a higher probability of positive PE among patients.

Diagnostic test:

Able to evaluate the status before symptoms becomes definitive

- Sens: P (Test + I Event+)
- Spec: P (Test – I Event -)

  Flip side to Sens and Spec are incorrect tests i.e. false negatives and false positives
- False positive: P (Test + I Event -) = 1-Specificity
- False negative: P (Test – I Event +)

Area under the curve is to be as high as possible for a good test.

Coordinates of the Curve

Test Result Variable(s): Scale has at least one tie between the positive actual state group and the negative actual state group.

Table 5. Association between the scores and actual outcome results

Positive if greater than or equal to[a]	Sensitivity	Specificity	1 – Sensitivity	Positive likelihood (LR+)	Negative likelihood (LR-)
-1.00	1.000	0.000	1.000	1.000	*
1.00	1.000	0.075	.925	1.081	-12.333
2.50	1.000	0.388	.612	1.634	-1.577
3.50	1.000	0.657	.343	2.915	-0.522
4.50	.970	0.821	.179	5.419	-0.181
5.50	.970	0.910	.090	10.778	-0.066
6.50	.939	0.940	.060	15.650	0.001
7.50	.909	0.940	.060	15.150	0.033
8.50	.818	0.955	.045	18.178	0.143
9.50	.727	0.970	.030	24.233	0.251
10.50	.606	0.970	.030	20.200	0.375
11.50	.485	0.985	.015	32.333	0.508
12.50	.303	0.985	.015	20.200	0.692
13.50	.091	0.985	.015	6.067	0.908
15.00	.030	1.000	.000	*	0.970
17.00	.000	1.000	.000	*	1.000
Average	.678	0.786	0.214	12.488	-0.653
Standard Deviation	0.377	0.334	0.334	9.868	3.298

[a]The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values. * Not applicable due zero denominator.

4 DISCUSSION

PE is one of the leading causes of mortality in pregnancy and postpartum in the world. No clinical prediction models have been validated yet in pregnancy (Armstrong et al 2017). Thus, any pregnant woman presenting with signs possibly consistent with pulmonary embolism is investigated radiologically.

As per hospital protocol, all de-identified patients had a chest X-ray done prior to PE diagnostic imaging (See Table 1). Depending on the chest X-ray report, patients had either VQ or CTPA done as a diagnostic image. During gestation, both modalities expose the foetus to radiation and CTPA confers an increased risk of breast cancer (Cutts et al 2013). Abnormal chest radiographs have been considered to affect the interpretation of ventilation of V/Q scans for the investigation of suspected pulmonary embolism, hence CTPA was chosen as the diagnostic method for the patients with abnormal chest x-ray (Arun et al 2011). Due to the reasons above CTPA in obstetrics is only performed in patients with an abnormal chest X-ray.

In comparison, VQ scan is less costly with less or no risk of increasing breast cancer risk, hence it is the most appropriate method for all patients with normal chest X-rays. However, according to WS Chan (2018), the rates of high probability VQ scans are much lower in the pregnant than in the non-pregnant population (<5 versus 20%), and, due to suboptimal imaging from altered contrast dynamics from increased cardiac outputs in pregnancy, CTPA can be nondiagnostic in up to 20% of pregnant patients.

In this study, majority of patients had normal chest X-rays, hence CTPA was only performed on seven (7) patients. However, for unknown reason, VQ scan was performed on one patient who had an abnormal chest X-ray (See Figure 1). A total of 34 (34%) were confirmed PE positive radiologically. Fortunately, as per hospital protocol, all these patients were initiated on LMWH (Clexane) therapeutic dose prior to diagnostic imaging. No mortality was recorded amongst these patients (See Figure 2). Reason could be that majority of these patients had either subsegmental or segmental type of PE which are structurally smaller in comparison to more aggressive types (saddle or lobal types.)

In contrast with the general population where PE occurrence is known to be influenced by age, this study found no statistical significance in PE occurrence between the age groups. According to Zhang et al (2020), history of positive previous PE/DVT increases the risk of PE in lifetime by 1.15% but surprisingly this study found no statistical association (P 0.629) between the two. The result might have been affected by only two of participants with previous DVT/PE during the study period.

Surgery and immobilization are known to be risk factors for PE across the whole population and in all age groups. Limited mobility in postoperative patients lead to stasis of blood and formation of blood clots (VTE/PE). During surgery, procoagulant tissue thromboplastin is released that converts prothrombin to thrombin and coagulation of blood (Pahlkotter et al 2020). Also in the postoperative period, there is low fibrinolytic activity and that increases the chance of blood coagulation. The study by Pahlkotter et al (2020) also found that PE is 2.5 times higher in patients who had emergency surgery than elective procedures. Strong association between surgery or immobilization and PE was confirmed by his study (P 0.0247). Therefore, early ambulation or mobility is a vital prevention measure for PE and thromboprophylaxis is highly recommended in all post-operative patients.

Vital signs were done by using electronic monitoring and they were all recorded. No statistical significance was found in association between PE and the vital signs. It was noted that about 20% of the patients had VQ or CTPA scans done based only on the finding of maternal tachycardia of 120bpm or more.

Goldhaber (2012) states that clinical predictors, such as body mass index (BMI), tachycardia, peripheral oxygen saturation and modified Wells score, may be used to identify women at higher risk of PE for imaging, but none had been sufficiently validated to support a recommendation for clinical use in pregnancy. In contrast, this study found that increased BMI is not associated with PE.

The association between PE and HIV infection either with viral load suppressed or not, was found to be statistically significant (P=0.021).

Van de Pol et al (2017) describes the increased level of oestrogen and clotting factors (V, VIII, IX, X and fibrinogen), venous stasis due to fetal compression of pelvic veins in pregnancy and reduced protein S as risk factors for embolism. While PE is increased to five times in pregnancy it is more frequent in the postpartum period (Cutts 2013). Unexpectedly, there was no difference found between antenatal and postnatal women who were diagnosed with PE in this cohort.

It was noted that during this study period there was a low number of patients with unilateral leg swelling (2), calf pain and tenderness (2) and unexplained sweating (7). Nevertheless, no association between these predictors and PE was found.

Normal physiological changes in pregnancy such as chest pain and dyspnoea make it difficult to diagnose pulmonary embolism (Cutts et al 2013). However, SOB, sudden onset of pleuritic chest pain and haemoptysis remain the most clinical predictive symptoms for PE in pregnancy and immediate post-partum.

Malignancy is one of the known risk factors for PE. Fortunately, during the study period, there was no participant with active/malignant history, hence, statistically significant calculations were impossible.

ABG and ECG in our setting (TBH) is part of initial work-up for every patient with symptoms suspicions of PE. A pregnancy cut-off value in antenatal patients was used in our study.

The study found a very strong association between PE and respiratory alkalosis (P 0.001), sinus tachycardia (P 0.0001) and Sl (P 0.001) Q3/T3 (P 0.0001).

There was no statistical difference was found between primiparous and multiparous women.

The modified Wells score (MWS) uses a simple stratification system of patients with a score of 4 or less being classified as ‘pulmonary embolism unlikely’ and a score of more than 4 as

'pulmonary embolism likely' (Cutts et al 2013). It demonstrated in the Christopher study, (Van Belle et al 2006) that the MWS had a high negative predictive value when combined with negative D-dimers (>99%) for prediction of PE in the nonpregnant population. But it has never been prospectively validated in pregnancy (Briony et al 2014).

5 CONCLUSION

It has been a challenge among obstetricians to predict PE in peripartum women as there is no clinical predicting tool validated yet. MWS combined with negative D-dimers has been validated only to be used in nonpregnant population.

In this study, there was a statistically significant ($P < 0.05$) association between PE occurrence and ten assessed factors (surgery in <4/52, immobilization >3/7, SOB, haemoptysis, sudden onset of pleuritic chest pain, respiratory alkalosis, sinus tachycardia, deep S1, Q3/T3 and HIV).

The PE clinical predicting tool has therefore been designed, whereby the score of 5 or less classified as PE unlikely/less likely while score of 6 and more, PE most likely. This tool may be used in pregnancy and postpartum to prevent unnecessary exposure to radiations and intervene when PE is most likely.

6 STRENGTH OF THE STUDY

Predicting tool is designed to use existing clinical information without exposing or re-exposing patients to the ionising imaging.

7 WEAKNESS AND CHALLENGES

The study is retrospective. It was a challenge to access all the patients' information on ECM as some folder pages were missing.

8 ACKNOWLEDGMENTS:

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9 ADDENDUM

9.1 Protocol: Clinical predictors of pulmonary embolism in pregnancy and immediate postpartum period.

Principal investigator

Dr IN Sheehama

Promoter

Prof H Botha

Introduction and motivation

Pulmonary embolism (PE) is a life-threatening, sudden occlusion of a lung artery as a result of a blood clot that was dislodged from somewhere else in the body, usually the legs (Armstrong et al 2017).

It is one of the leading causes of mortality in pregnancy and immediate postpartum in the world. No clinical prediction models have been validated yet in pregnancy.

Thus, any pregnant woman presenting with signs possibly consistent with pulmonary embolism is investigated radiologically.

According to Van de Pol 2017, the increased level of estrogen and clotting factors (V, VIII, IX, X and fibrinogen), venous stasis due to fetal compression of pelvic veins in pregnancy, reduced protein S, reduced fibrinolysis in pregnancy, pulmonary embolism has been found to be five-fold high in pregnancy (Cutts et al 2013). Normal physiological changes in pregnancy such as chest pain and dyspnea make it difficult to diagnose pulmonary embolism.

D-dimers also rise gradually throughout pregnancy and normal cutoff values for D-dimer assays have not been validated in pregnancy. Thus why, the diagnosis of pulmonary embolism in pregnancy is usually based on computed tomography pulmonary angiography (CTPA) and ventilation perfusion scanning (VQ scans). However, according to WS Chan (2018), the rates of high-probability VQ scans are much lower in pregnancy than in the nonpregnant population (<5

versus 20%), and due to suboptimal imaging from altered contrast dynamics from increased cardiac outputs in pregnancy, CTPA can be nondiagnostic in up to 20% of pregnant patients.

During gestation, both modalities expose the fetus to radiation and CTPA confers a 14% increased risk of breast cancer (Cutts et al 2013). Hence, a system that stratifies pregnant women as low risk pulmonary embolism and hence avoids unnecessary imaging would be ideal.

Non radiological options

The modified Wells score (MWS) has a simpler stratification system of patients with a score of 4 or less being classified as 'pulmonary embolism unlikely' and a score of more than 4 as 'pulmonary embolism likely' (Cutts et al 2013).

It is proven in the Christopher study, that the MWS had a high negative predictive value when combined with negative D-dimers (>99%) for prediction of pulmonary embolism in the nonpregnant population. But it has never been prospectively validated in pregnancy (Briony et al 2014.)

Goldhaber (2012), states that clinical predictors, such as Body Mass Index, complications of pregnancy, previous venous thromboembolism, peripheral oxygen saturation and modified Wells score, may be used to identify women at higher risk of PE for imaging, but none had been sufficiently validated to support a recommendation for clinical use.

Pulmonary embolism (PE) being one of the leading causes of death in pregnancy and postpartum, women who appropriately diagnosed and treated PE have a low risk of adverse outcome. Furthermore, the outcome for the fetus depends on the outcome for the mother. However, the investigations used to diagnose PE (VQ scanning or CTPA) carry risks of radiation exposure, reaction to contrast media and false positive diagnosis and can cause unnecessary psychological distress to the patients.

MRI has the potential to avoid radiation exposure, but no sufficient evidence to support inclusion in guidelines. Therefore, clinicians face a challenge when deciding whether to use diagnostic imaging to investigate patients for suspected PE in pregnancy and postpartum and between risking potentially catastrophic consequences of missed diagnosis if imaging is withheld and risking iatrogenic harm if imaging is over used. (Armstrong et al 2017)

Aim

- To describe clinical markers for suspicious PE amongst pregnant mothers and immediate postpartum and to design a practical clinical tool for accurate diagnosis of PE in peripartum in our population.

Objectives

- To evaluate performance of PE scoring system that can be utilized in our environment and other settings.
- To evaluate the requested images done for suspicious PE in pregnant and immediate postpartum mothers in **Tygerberg Academic Hospital (TBH).**

Potential benefits of the Study

- In our current environment of economic crisis with inadequate and unavailability of medical resources, it would be a great achievement if clinical predictors of PE in pregnancy and immediate postpartum period can be determined and used as a diagnostic tool of PE. This would save a lot of lives as those who will be graded as most likely PE can be initiated on therapeutic anticoagulant prior referral/ prior imaging.
- Secondary, it will be cost effectiveness and also prevents unnecessary exposure to moms of radiation risking them at increased chance of breast cancer and negative effect to the unborn fetus.

Methodology

The study will be performed as a retrospective and analytical study over 48 months, from the Obstetric Unit at Tygerberg hospital, a secondary and a tertiary referral center. The research will describe all the images done for suspicious PE in pregnant and immediate post-partum mothers. The patient's files (max 150) who were suspected of having PE and underwent imaging (V/Q scan or CTPA) will then be retrospectively evaluated by looking at the clinical picture they presented with. The files will be categorized into 2 parts, those who were diagnosed PE positive and PE negative. Description of type of PE which dominated will also be described. Initiation of anticoagulant in PE positive patients, whether they were initiated the time of presentation or only at the time of confirmed diagnosis.

Inclusion

All obstetric patients who were imaged for suspected PE (delivered, undelivered and immediate postpartum (3 to 5 days) admitted to F2, C2A, OCCU, J2, J4 and J5.

Target of total no 100-150 patients is aimed at.

Certain factors will be looked at and their implications on an individual in developing PE (see the appendix for parameters)

Request for V/Q or CTPA

Exclusion

All non-obstetric patients, patients already known with PE or varicose thrombosis.

Statistical Analysis

Descriptive statistics will be used. The data will be captured in Excel and the statistical analysis will be performed using standard techniques with the help of a bio-statistician. For continuous variables means with standard deviations will be calculated for normally distribution data, and medians, with ranges and interquartile ranges, will be calculated for skewed data. Categorical data will be presented as frequencies and percentages, and the Chi-squired test and the Fisher's exact test at a significance level of p=0.05 will be used to test for any association between the variables.

Publication Plan

The study will first be submitted as an MMed dissertation and following that, a publication in a South African journal is planned.

Ethics

The study will be approved by the Health Research Ethics Committee of Stellenbosch University and Tygerberg Hospital. As the study is retrospective approval will be sought from the Health Research Ethics Committee of Stellenbosch University for waiver of consent. All the information will be kept anonymous and will be used to trace patient's medical history.

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9.2 Questionnaire

TABLE 1: PARAMETERS

AGE: _____

HISTORY:

1. Previous DVT / Pulmonary embolism	YES ☐	NO ☐
2. Surgery in previous 4 weeks	YES ☐	NO ☐
3. Immobilization for >3 days	YES ☐	NO ☐

VITAL SIGNS (specify):

Pulse rate _____

Blood pressure _____

Respiratory rate _____

Temperature _____

CLINICAL SIGNS AND SYMPTOMS OF DVT:

Calf pain and tenderness	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐
Unexplained unilateral leg swelling	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐
Tachycardia	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐
SOB	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐
Unexplained sweating	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐
Hemoptysis	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐
Sudden onset pleuritic chest pain	ABSENT ☐	PRESENT ☐	NOT RECORDED ☐

ABG (quantify): NOT DONE/MISSING

Ph _____

PO2 _____

PCO2 _____

HCO- _____

BE _____

MALIGNANCY (specify):

ECG	YES ☐	NO ☐	NOT DONE/MISSING ☐
Sinus tachycardia >120bpm	YES ☐	NO ☐	NOT DONE/MISSING ☐
Deep S wave in I	YES ☐	NO ☐	NOT DONE/MISSING ☐
Deep T wave in III	YES ☐	NO ☐	NOT DONE/MISSING ☐
Deep Q wave in III	YES ☐	NO ☐	NOT DONE/MISSING ☐

BMI: _____

HIV STATUS: _____

PARITY: _____

MODE OF DELIVERY: _____

CHEST X-RAY: Normal ☐ Abnormal (specify) ☐

9.3 PULMONARY EMBOLISM CLINICAL PREDICTING TOOL(SCORING SYSTEM)

Predictors	**Score per predictor (circle if present)**	**0 score if absent**

10 SURGERY < 4 WEEKS	1	
11 IMMOBILIZATION FOR > 3 DAYS	1	
12 SHORT OF BREATH	3	
13 HAEMOPTYSIS	2	
14 PLEURITIC CHEST PAIN	3	
15 RESPIRATORY ALKALOSIS	2	
16 TACHYCARDIA	2	
17 ECG : SINUS TACHYCARDIA	1	
18 ECG: S1/T3/Q3		
• S1 (deep S wave in lead I)	1	
• Q3 (prolonged Q in lead III)	1	
• T3 (inverted T in lead III)	1	
19 HIV	1	
PATIENT'S TOTAL SCORE		
PE most likely (6 or more)		
PE less likely (5 or less)		

See below a general histogram on the distribution of the scale/scores across all the women.

These scores were a sum of the assigned points across each significant variable. Indicating that 5 women (frequency on the y-scale) had scored 0 points across all statistically significant predictors. The highest frequency (of women) were between 0-5 points i.e. most often these were women without PE (actual outcome) and on the predictor points scale had 5 points of less.

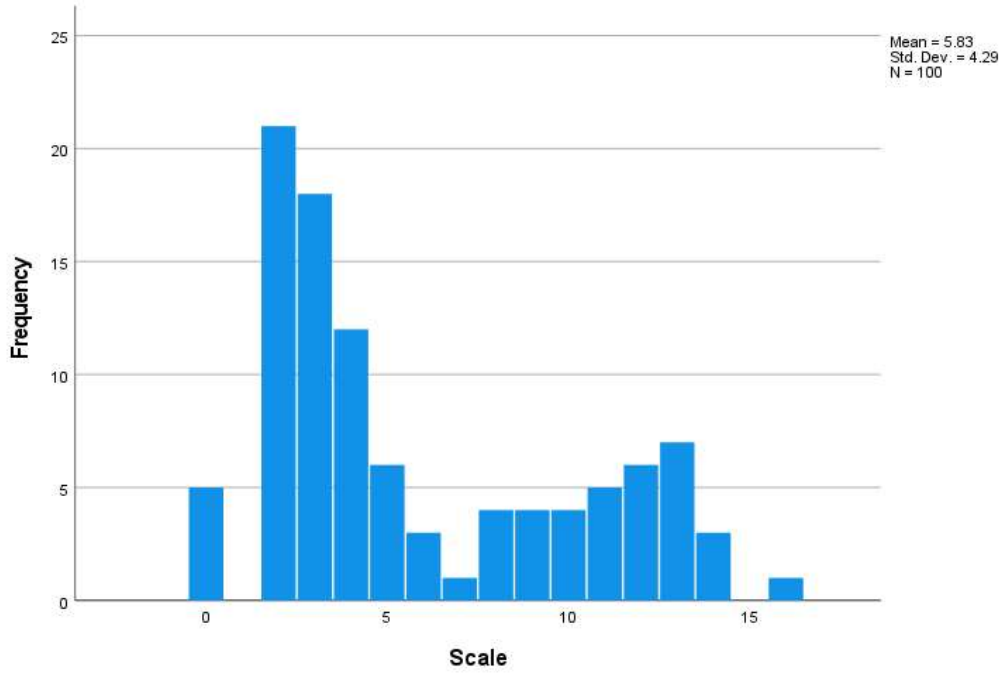

Figure 3: Histogram depicting the distribution of points (scale) among the population of women (frequency) who were either pregnant/≤1 week postpartum either positive or negative for pulmonary embolism

Area under the curve is to be as high as possible for a good test.

Coordinates of the Curve

Test Result Variable(s): Scale

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
-1.00	1.000	1.000
1.00	1.000	.925
2.50	1.000	.612
3.50	1.000	.343
4.50	.970	.179
5.50	.970	.090
6.50	.939	.060
7.50	.909	.060
8.50	.818	.045
9.50	.727	.030
10.50	.606	.030
11.50	.485	.015
12.50	.303	.015
13.50	.091	.015
15.00	.030	.000
17.00	.000	.000

The test result variable(s): Scale has at least one tie between the positive actual state group and the negative actual state group.

a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.