Optimization of lung scintigraphy in pregnant women at The Ottawa Hospital

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Section 1: A Retrospective Cohort Study

Abstract

TITLE: Optimization of lung scintigraphy in pregnant women at the Ottawa Hospital.

INTRODUCTION: Pulmonary embolism (PE) is a major cause of mortality during pregnancy. It is estimated that 20% of maternal deaths in the United States are due to PE. A lung V/Q study in a standard (non-gravid) patient typically consists of a low dosage ventilation study followed by a higher dosage perfusion study. In some centers however, perfusion-only imaging, without accompanying ventilation imaging has been employed. In this method, a several-fold lower dose of radioactivity is used. Perfusion-only imaging has multiple advantages. In addition to reduction of radiation dose to the mother and the fetus, there is decreased cost to the health-care system as well as improved patient convenience and shortened hospital workflow.

OBJECTIVES: The present study aimed at assessing the negative predictive value (among other diagnostic accuracy measures) of perfusion-only imaging in a large group of pregnant patients with suspected pulmonary embolism.

METHODS: This study was a retrospective cohort study of the entire pregnant patients with suspected PE who underwent V/Q scan at The Ottawa Hospital and their V/Q scans were available in the PACS system. After acquiring REB approval, a comprehensive search in the PACS (Picture Archiving and Communication System) was conducted to find pregnant patients who were assessed for PE in our division since 2004 (the earliest date the V/Q images were available in our system). A statistical consultation was made before the initiation of data collection and at the time of data analysis. All patients who

met the inclusion criteria were included. Initially a nuclear medicine resident with 2 years of experience read all the perfusion- only images. The PISAPED criteria were used for image interpretation. Then the results were compared against the reports made by nuclear medicine staffs that were available to us in our electronic system and a final interpretation was made after such comparison. The follow-up clinical notes were used as the gold standard to make a final diagnosis of PE. Finally, diagnostic accuracy measures were calculated.

RESULTS: A total of 364 patients were included. Mean maternal age at the time of lung V/Q scan was 30.3 years-old (SD=5.8) ranging from 16 to 51 years-old. From a total of 362 lung perfusion scans, 316/362 (87.3%) scans interpreted as normal, 17/362 (4.7%) scans were interpreted as high probability and 29/362 (8.0%) scans were interpreted as non-diagnostic. Pulmonary embolism was diagnosed in a total of 15 patients directly after performing lung scan. None of the patients with normal perfusion-only scans were diagnosed later with PE, proving a negative predictive value of 100%. The sensitivity and specificity of perfusion-only imaging after including the non-diagnostic studies were 100% (100% to 100%) and 99.1% (88.1% to 94.1%), respectively with a negative predictive value of 100% (100% to 100%) and a positive predictive value of 32.6% (19.1% to 46.2%).

Conclusion: The results of the current study show that perfusion-only imaging has a very high negative predictive value for PE in pregnant population and therefore can exclude PE with a very high degree of accuracy**.**

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Chapter 1: Introduction

1.1 Introduction to the thesis

Pulmonary embolism (PE) is a serious health problem which occurs when a blood clot that is usually formed in the lower extremities moves within the vasculature and lodges in the pulmonary arteries. Pulmonary embolism during pregnancy is considered a serious health issue with potential significant fatal consequences as a result of blocking pulmonary blood flow. Currently, at The Ottawa Hospital (TOH), scintigraphic lung ventilation-perfusion scans are performed to rule out PE in pregnancy. The present analysis is an attempt towards chasing practice at TOH by utilizing perfusion-only lung scan in pregnant patients suspected of having PE.

Introduction to pulmonary embolism in pregnancy

1.1.1 Definitions and Etiologies

Pulmonary embolism is caused by blockage of the pulmonary arteries by substances that originate elsewhere in the body. Possible causes of blockage include blood clots (thrombi), air and fat. Among them, thrombi are much more frequent and therefore more commonly encountered in medical practice. Formation of blood clot is more common in patients with certain medical conditions such as cancer, post-surgery, increased tendency to form clots (thrombophilia) and pregnancy, the latter of which will be the focus of this thesis.

Pulmonary embolism is considered a potentially fatal condition because it can block blood flow to the heart, impair blood oxygenation, produce hypoxemia and in severe cases trigger cardiac arrest.

As mentioned above, pregnant patients are at increased risk of developing deep vein thrombosis (DVT) and consequently PE. This is due to the fact that all three elements of Virchow's triad, venous stasis, vascular damage and hypercoagulability, may all be present during pregnancy (1). Venous stasis occurs due to increasing levels of progesterone during pregnancy, compression of the draining vasculature by the gravid uterus and finally, compression of the iliac veins by pulsatile iliac arteries. As for vascular damage, it is essentially caused by prior vaginal or instrumentation deliveries. Also, mainly due to the fact that body is preparing for the upcoming delivery, its associated hyper-coagulation state is seen in pregnancy, partially caused by reduced activity of protein S and increased levels of protein C. Other factors include amplified fibrin production, reduced fibrinolysis activity, increasing levels of coagulation factors II, VII, VIII and X as well as resistance to activated protein C. (1, 2)

Specifically, decreased blood flow in the legs, predisposes pregnant patients at increased risk of developing blood clots in the leg veins. Individuals with inherited coagulation disorders, prior history of antiphospholipid syndrome, prior history of a thrombotic disease and obesity are at even more increased risk

of developing blood clots (2). These blood clots are considered a major source of thromboembolic episodes. The substantially increased coagulability experienced during pregnancy, is associated with increasing levels of coagulation activation markers such as D-Dimer.

1.1.2 Epidemiology of PE in Pregnancy

In the developed world, pulmonary embolism is a major cause of mortality during pregnancy and up to 6 weeks following delivery (3). It is estimated that 20% of maternal deaths in the United States are due to PE (4). Pregnant women are five times more likely to develop PE compared to non-pregnant women (5). In Canada, PE is accounting for 20.5% of direct maternal deaths, according to the statistics by Health Canada (42).

1.1.3 Diagnosis of PE in pregnancy

The clinical diagnosis of PE is generally challenging, mainly due to the absence of specific signs and symptoms. The challenge is even greater in pregnant women, because any false positive or false negative results have significant patient management consequences. False positive results in pregnant patients impact their delivery options, post-delivery contraception choices as well as prophylactic treatments for future pregnancies. On the other hand, false negative results prevent patients from obtaining needed treatments, putting patient at increased levels of mortality risk (a mortality risk of 30%) versus those patients who receive the appropriate treatments (a mortality risk of 8%). (1)

Bayes' Theorem: Bayes' theorem or theorem of conditional probability states that the examination results regarding the presence or absence of a disease depend on pretest probability in addition to the test's power. The probability that a patient has a disease before undergoing an examination is defined as pre-test probability. If no additional disease-pertinent information exists, the pre-test probability directly equals the disease prevalence. When available, other patient characteristics such as additional clinical history and other clinical and examination results are also taken into consideration to form the prior probability. (23)

Well's Criteria: The Well's clinical decision rule, which is a clinical tool to assign a pretest probability in patients suspicious of having PE has not been validated in pregnant patients (6). In addition, accuracy of the D-Dimer test, which is a very sensitive blood test for ruling out PE, has not been explored in pregnancy. (7)

A scintigraphic lung V/Q study in a non-gravid patient typically consists of a low-activity ventilation study followed by a higher-activity perfusion study; the greater activity is needed to render relatively negligible residual activity from the prior ventilation study. The ventilation phase consists of the patient inhaling approximately 18-37 MBq of ^{99m}Tc-technegas particles followed by imaging the resulting distribution in the alveoli. This is then followed by the perfusion phase which consists of the intravenous administration of approximately 185 MBq of the ^{99m}Tc-macro aggregated albumin (MAA) followed by imaging of the resulting

distribution of the radiopharmaceutical in the lung arterioles. In this manner, a comparison of the two physiologic processes of ventilation and perfusion can be obtained.

Imaging of the distribution of ventilation and perfusion examinations can be conducted by planar or tomographic (SPECT) imaging. With the planar method, currently performed at the Division of Nuclear Medicine at TOH, studies are traditionally reported as normal or high, intermediate or low probability of PE, based on the well-recognized PIOPED criteria (8). A normal V/Q study effectively rules out PE.

In the general population, V/Q studies are frequently indeterminate for PE, however, this is not the case in pregnant patients. One publication showed that about 75% of V/Q studies in pregnant patients are reported normal, 20% indeterminate and 5% high probability (9). According to the current practice guidelines, a recent chest radiograph within 24 of the V/Q scan is recommended to exclude patients with abnormal chest radiographs which drops the rate of indeterminate reports (13).

1.1.4 Ventilation/Perfusion Scan in Pregnancy

Guidelines have been developed to guide clinicians when assessing PE in pregnancy. Some of these guidelines include British Thoracic Society guidelines for the management of suspected acute pulmonary embolism, American College

of Chest Physicians evidence-based clinical practice guidelines, ESC Guidelines on the diagnosis and management of acute pulmonary embolism as well as American Thoracic Society/Thoracic Radiology Clinical Practice Guidelines.

According to American Thoracic Society/Thoracic Radiology Clinical Practice Guidelines, for example, the clinical indications for performing imaging for assessment of PE during pregnancy include the following: shortness of breath, pleuritic chest pain, hypoxemia, increased heart rate, and less frequently, increased respiratory rate, blood in the sputum, syncope, coughing, unexplained hypotension, and non-specific chest pain (13).

Imaging modalities are the only tools to evaluate PE in pregnancy. The two main imaging modalities available for evaluation of PE in pregnancy are CT Pulmonary Angiography (CTPA) and lung ventilation-perfusion scintigraphy (V/Q scan). Doppler ultrasonography of the leg veins are also performed to assess presence of thrombosis which is usually the cause of pulmonary embolism.

Several different approaches to V/Q scintigraphy in pregnant women exist. Many centers perform both ventilation and perfusion phases, though the administered activity may be reduced by half, which in turn would decrease radiation exposure by half. In other centers perfusion-only imaging without accompanying ventilation ruled out in a patient with normal V/Q scan. Patients with high probability studies usually end up receiving anticoagulation treatment.

The challenge remains when the scan is reported as indeterminate. In these patients where the management options include either treating the patient or performing CTPA, the pretest probability plays a major role. If suspicion is high, the patient can be treated with anticoagulation therapy. However, when there is low clinical suspicion for PE, treatment should be withheld. Those patients with clinical uncertainty as to what is causing their symptoms are the ones who will benefit from subsequent CTPA (20).

1.1.5 Perfusion-only imaging

Prior studies, in the general population and using PISAPED criteria, have shown the sensitivity of a ‘‘PE present’’ perfusion scan being 80.4% (95% CI of 75.9%284.3%) and the specificity of ‘‘PE absent’’ scan being 96.6% (95% CI, 95.5%297.4%) with the proportion of ‘‘indeterminate’’ cases being 0% (95% CI, 0.0%20.2%). (40)

With perfusion-only imaging, the sensitivity of the lung scan should be preserved and its negative predictive value (the probability that patient is not affected by the disease given examination results are negative) should remain high. (23) Specificity, on the other hand, may decrease as does positive predictive value (10, 11, 12). In perfusion-only imaging, if a perfusion defect is encountered on the perfusion images, typically a ventilation scan is requested the next day, following decay of the radiotracer used in perfusion activity. This would offer a lower radiation exposure compared with performing CTPA to clarify the defects seen on

the perfusion-only images; although a period of follow up (a few months) is needed to render a final diagnosis.

There are certain advantages inherent in perfusion-only imaging such as reducing the risk of radiation to mother and her fetus, decreasing the cost to the health-care system, improving patient convenience and accelerating workflow in the nuclear medicine departments. However, there is limited evidence available on the use of perfusion-only lung scintigraphy for the exploration of PE in pregnancy. In addition, variable patient demographics may limit the generalizability of the results of existing cohort studies.

PISAPED Criteria: The Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISAPED) trial proposed a set of diagnostic criteria known as PISAPED diagnostic criteria for the interpretation of perfusion-only imaging intended to diagnose or exclude PE (22). The study used the perfusion-only images in addition to the chest X-Ray of the patients. Based on PISAPED diagnostic criteria, the perfusion-only examinations are independently categorized as "normal", "near normal", "abnormal compatible with PE" (single or multiple wedge-shape perfusion defect compatible with PE, or "abnormal not compatible with PE" (perfusion defects other than wedge- shape defects).

Table1. PISAPED perfusion-only scan interpretation criteria

Abnormal suggestive of	Presence of single or multiple

PE	wedge- shaped perfusion defects, the size of which corresponds to that of lobar, segmental or sub segmental regions of the lung
Normal Scan	No perfusion defects
Near normal	Presence of impressions caused by enlarged heart, hila, or mediastinum or an otherwise normal scan
Abnormal, not suggestive of PE	Presence of single or multiple other than wedge-shaped perfusion defects
Nondiagnostic	All other findings or poor image quality

1.1.6 Risk of radiation

Overall, ventilation/perfusion lung scintigraphy results in low levels of radiation exposure. The effective whole body dose for a ventilation/perfusion study is estimated to be 1.4-2.0 mSv, which is lower than the amount of radiation exposure by CTPA (2.2-6.0 mSv) (12, 14, 39). Although, the amount of radiation received by the fetus is considered low (less than 1 mGy) with either CTPA or V/Q study, utilization of diagnostic imaging for suspected PE in pregnancy remains constrained due to inherent risk of radiation to both mother and the fetus (12,14, 39).

Both V/Q scan and CTPA are associated with radiation to the mother and the fetus. CTPA is associated with moderately elevated amounts of radiation to the breast tissue in pregnant women. The amount of radiation to the breast tissue by CTPA is estimated at 10-70 mGy and by V/Q scan, less than 1.5 mGy (14). As a

result, V/Q scintigraphy has been recommended by the American Thoracic Society as the initial examination in pregnancy (13). This is important, as the breast tissue is more radiosensitive in young women, due to increased size during the pregnancy, and hence radiation exposure should be minimized.

The radiation received by the fetus early into the pregnancy has been estimated at 10 mrad for each millicurie of activity of 99mTc labeled MAA (15). Some literature has estimated that the amount of radiation received by the fetus is higher for V/Q scan than CTPA. For instance, Winer-Muran showed that the mean fetal dose by CTPA was less than 0.01-0.66 mGy, versus 0.1-0.8 mGy for V/Q scan (16). It has to be noted that all general estimations and doses are significantly lower than radiation thresholds that may cause adverse genetic outcomes (0.05 Gy) (19). Prior studies have reported that the estimated increased risk of cancer development in fetuses exposed to standard doses of 99mTc as a result of ventilation examination reaches 1.3 per million, while the pertinent number for perfusion examination reaches 0.6 per million, which shows relative increased risk of cancer development as a result of ventilation, compared with perfusion (20). Another study from 1990 by Mole calculated an odds ratio of 1.23 (with 95% confidence interval of 1.04 -1.48) for childhood cancer after a mean fetal whole-body dose of 6 mGy. (26) It would therefore be beneficial to decrease the amount of fetal exposure to radiation by performing perfusion-only examinations.

Although, the amount of radiation received by the mother and her fetus as a result

of a standard V/Q study is considered reasonable for the indication. This is because the maternal and fetal consequences as a result of missing a PE diagnosis would be much worse than the very minimal risk of radiation-related cancer (11, 20). According to the principle of ALARA extra efforts are demanded to reduce radiation exposure to both mother and her fetus (18). Indeed, many patients referred for a V/Q study have concerns about the risk of radiation, especially to their fetuses.

1.2 Statement of the problem at The Ottawa Hospital

Proposed methods of using half dose ventilation and perfusion pharmaceuticals in pregnant patients or performing perfusion-only studies to decrease the amount of radiation received by the mother or the fetus have been previously introduced and discussed in the literature (20). The current practice at The Ottawa Hospital (TOH) in the surveying for suspected pulmonary emboli in pregnant patients is performing ventilation-perfusion lung scans. To perform this examination, radioactive drugs, called radiopharmaceuticals, are used which expose patients and their fetuses to a minimal yet negligible amount of radiation.

To lower the amount of radiation received by the patients and their fetuses, different changes to the standard ventilation-perfusion examination have be proposed and examined. At TOH, a half-dose method is used which means a half-dose of the standard dose of radiopharmaceuticals is used in pregnant patients. To even further lower the amount of radiation received by these patients,

perfusion-only imaging could be performed where instead of performing ventilation and perfusion imaging, only perfusion imaging is conducted. In this thesis, the diagnostic accuracy of perfusion-only imaging for the assessment of PE in pregnant patients, with an emphasis on its negative predictive value, will be assessed.

1.3 Review of previous literature

There is limited literature on perfusion-only imaging for assessment of PE in pregnancy and most of the available literature on the assessment of PE in pregnancy has utilized ventilation/perfusion imaging. We conducted a systemic literature search to capture the available literature published on this topic. Table 2 summarizes the characteristics of the studies we found pertinent to our research topic.

Table2. Summary of study characteristics of the limited included studies

Author	Year	Study Design	Study Population	Modality	Test Performance/Findings
Balan et al. (20)	1997	Retrospective Cohort	82 pregnant women	Ventilation/Perfusion Scan	38% normal 23% low 17% intermediate 22% high

Chan et al. (9)	2002	Retrospective Cohort	120 consecutive pregnant women suspected of having PE and had presented to the emergency department	Ventilation/Perfusion Scan	73.5% were interpreted as normal 24.8% as non-diagnostic 1.8% as high probability
Scarsbrook et al. (11)	2006	Retrospective Cohort	105 pregnant patients presented with signs and symptoms of PE over 5 year period	94 patients had Perfusion-only Scans 9 patients had CTPA 2 patients had both V/Q and CTPA	P-only: 92% Normal, 1% High Probability, 7% Non-Diagnostic
Shahir et al. (10)	2010	Retrospective Cohort	199 pregnant patients suspected of having PE	93 underwent perfusion-only imaging 100 patients underwent CTPA 6 patients underwent both	96 out of 99 had normal P-only scans, 0 patient had high probability scan, 3 patients had indeterminate scans, negative predictive value of 100%
Revel et al. (21)	2011	Retrospective Cohort	91 pregnant patient underwent V/Q (for assessment of PE) 46 pregnant patients underwent CTPA (for assessment of PE)	Ventilation/Perfusion Scan and CTPA	V/Q scan: 11% Positive, 70% Negative, 19% Indeterminate CTPA: 16% Positive, 65% Negative, 19% Indeterminate

In 1997, a retrospective cohort study by Balan et al. reported the findings of ventilation/perfusion scans in 82 pregnant women (20). The study included pregnant women retrospectively studied over a 5-year period. The distribution of PE probability was 38% normal, 23% low, 17% intermediate and 22% high. Patients with high probability of PE were all treated with anticoagulation therapy post V/Q scan. 86% of patients with

intermediate probability for PE and 6% of those with low probability of PE were also treated with anticoagulation therapy. No therapy was given to any of the patients with normal V/Q scan during the entire follow up period. The study demonstrated a lower rate of normal V/Q scans as compared with the study by consequent studies (9) with comparatively increased proportion of low and high probability examinations which may be related to different demographic of included patients in the study with or without technical differences. As noted above, the study used V/Q scans and not perfusion-only imaging.

Chan et al. published a retrospective cohort study in 2002 comprising 120 consecutive pregnant women who had presented to the emergency department and deemed suspected of having PE (9). Patients were assessed by V/Q scans using 99mTc-MAA for perfusion and technetium Tc 99m methylene diphosphonate aerosol (99mTc-MDA) and technetium Tc 99m sulfur colloid (99mTc-SC) for ventilation imaging. Images were interpreted by two independent imaging professionals. From a total of 120 image series, 87 cases (72.5%) were read as normal, 29 cases (24.2%) were read as non-diagnostic and 4 cases (3.3%) read as high probability for PE. The article concludes that a very small proportion of pregnant patients end up having a high probability V/Q scan. The numbers were substantially different than what was seen in the non-pregnant patient population, with

comparatively increased number of normal scans in pregnant women (72.5% normal scans in pregnant patients vs. about 33% normal scan in non-pregnant patient population). (9) The lower proportion of non-diagnostic examinations in pregnant women as compared with non-pregnant patients (24.2% vs. 50%) is most likely related to their age (pregnant patients are generally young adults with no or minimal lung pathologies). Lung pathologies produce abnormal perfusion scans and therefore are considered a main cause of non-diagnostic V/Q scans. The low rate of high probability scans during pregnancy can be associated

with the fact that most of the time, symptoms experienced during pregnancy such as chest pain or shortness of breath, are not caused by PE but rather by pregnancy itself. Even though the study reports a high number of normal ventilation- perfusion scans during pregnancy, it is unclear what would be the number if perfusion-only examination was conducted. Also, chest radiograph was performed only in 60 cases (49.6%) with about 40% of those chest X-rays being abnormal. This is not in keeping with the current guidelines that recommend performing ventilation-perfusion scans in pregnant patient with normal chest X-ray and performing CTPA in those with abnormal Chest X ray. Finally the study shows that none of the patients with normal V/Q scan was later diagnosed with PE (0 of 80 women; 95% CI of 0-1.2%), proving that a normal scan can safely exclude PE during pregnancy.

A third retrospective cohort study by Revel et al., published in 2011, analyzed V/Q scans (total of 91) and CTPAs (total of 46) performed in pregnant patients (21). The percentage of [positive/negative] studies (for assessment of PE) were [16%/65%] for CTPA and [11%/ 70%] for lung V/Q studies with the rate of indeterminate scans being similar (19%) for both imaging procedures. The mean total radiation received by the mother were 7.3 for CTPA and 0.9 mSv for V/Q scan scintigraphy. The study concludes that lung scintigraphy and CTPA perform comparably for the diagnosis of PE in pregnant patients with no significant difference in the positive, negative or indeterminate result proportions. According to the authors, what makes the difference between the two procedures is the maternal radiation dose with radiation dose being higher with CT angiography warranting CTPA protocol modifications. Again, as noted, the study utilized V/Q study for the assessment of PE in pregnancy and not perfusion-only imaging.

All above three studies used V/Q scans for the assessment of PE in pregnancy. Scarsbrook et al. (2006) however assessed efficacy of perfusion-only examination for ruling out PE in pregnant patients. (11) The retrospective cohort study included a total of 105 pregnant patients who had presented with signs and symptoms of PE over a five-year period. 94 of these patients were assessed by perfusion-only examination, 9 by CTPA and 2 by both imaging procedures. 92% of the perfusion-only scans were reported as normal, 7% non-diagnostic and 1% as high probability for PE. Two patients with non- diagnostic scans underwent CTPA

and were found negative for PE. These two patients were found to have pulmonary consolidation and were treated for pneumonia. None of the patients with non-diagnostic lung scans were treated with anti-coagulation therapy. In fact, no patient with a normal or non- diagnostic perfusion-only scan was found to have PE on the follow up period. In this study the incidence of PE in pregnancy was measured at 3% (3 out of 105). The study concluded that the performance of perfusion-only imaging in pregnant patients is reasonable given that the majority of scans were normal. Again, the study concluded that to achieve a lower number of non-diagnostic examinations, patients with underlying lung pathology or those with abnormal chest X-Ray should be assessed by other radiological modalities.

In 2010, Shahir et al. published a retrospective cohort study on pregnant patients suspected of having PE, who underwent CTPA or perfusion-only imaging. (10) The study did not include patients with history of DVT or postpartum patients. A total of 199 patients were included in this study. 93 patients underwent perfusion-only imaging, 100 patients were examined by CTPA and six patients by both. Perfusion scans were conducted post administration of a reached dosage of 37-55 MBq of 99m-Tc labelled MAA. Patients were imaged for a duration twice the usual, in order to achieve a standard photon count of 500,000 counts/projection. The authors used modified PIOPED I criteria for image interpretation. They used a threshold of 1.5 segmental perfusion defect in in order to call a high probability scan. Patients were followed for a period of three months after the initial perfusion scan. A total of 96 patients (out of 99 patients who underwent perfusion

scan) had negative findings on the scan (63 scans were normal, 14 were very low probability and 19 low probability). No single patient was diagnosed with high probability of PE. Three of the scans were indeterminate, two of which had no PE on the subsequent CTPA and the third one had uncompleted CTPA examination. None of the patients with normal perfusion scan developed PE on the clinical follow-up, showing a negative predictive value of 100% of perfusion-only examination.

As can be seen all above studies are subject to limitations associated with retrospective methods among which are patient selection and patient assignment for different imaging modalities. In addition, it can be imagined that the currently utilized guidelines for assessment of PE in pregnancy differ from those used 5 or 10 years ago. In all above studies, patient assignment to each imaging modality was done based on clinical judgement. Also, at the time the above mentioned studies were conducted, D-Dimer test was used variably, causing alterations in patient selection compared to the contemporary practice, where routine use of D-Dimer for assessment of PE in pregnancy is not recommended, due to high levels of false positive results (13). More importantly, only two of the studies discussed above utilized perfusion-only examination in pregnancy and the rest of the studies had used V/Q scans. Also, concerns remain about the interpretation criteria used in the above studies. For example, Shahir et al used modified PIOPED I criteria using a minimum of 1.5 mismatched segmental defect as a cut off value for high

probability perfusion only scan, which is quite different from the cut off of 1 mismatched segmental defect used in PISAPED interpretation guidelines. Therefore, studies interpreted earlier than 2006 could have been interpreted differently if the current guidelines were applied.

1.4 Rational for the study

Pregnant patients suspected of having PE are frequently referred to the nuclear medicine department for ventilation/perfusion scan. The alternative method to ventilation/perfusion scan in pregnancy is perfusion-only scan, with a much lesser radiation exposure for both patient and her fetus, among other benefits mentioned earlier. Although this method has been in use for many years in some centers around the globe, there is limited literature available on this topic. In addition, the available limited literature is remote and no recent study has validated the diagnostic performance of perfusion- only method in the evaluation of PE in pregnancy. There has also been some variability in the diagnostic performance of perfusion-only imaging in the limited literature, which is most likely due to different patient characteristics, among other effects.

Considering the fact that perfusion-only imaging exposes patients to a lesser amount of radiation and it has shown a good level of efficiency, it appears necessary to assess the diagnostic performance of this method. Therefore, we decided to objectively assess the diagnostic performance of perfusion-only imaging, in particular its negative predictive value, using the current practice

guidelines in a large pool of patients who were referred to the Department of Nuclear Medicine at The Ottawa Hospital.

Based on the available evidence, perfusion-only imaging has a high negative predictive value (10, 11). However, considering the fatal consequences of missing PE, if switching from currently performed V/Q scan method to the perfusion-only method is considered, it has to be proved that perfusion-only imaging has a comparable negative predictive value for excluding PE in pregnancy. This is because a high negative predictive value has direct impact on patient safety and patient care. In other words, it has to be ensured that if PE was ruled out on perfusion-only scans, the patient remains PE free during the 90-days interval post scan. A 90-day follow-up period post initial visit is reasonable and mandatory as it is possible that either the V/Q scan or the perfusion-only scan missed an underlying PE and therefore by following up patients, a missed diagnosis would be revealed to the clinicians. If PE occurs after the period of 90 days, it is assumed unrelated to the initial episode. Evidence is needed that shows perfusion-only imaging is comparable to ventilation/perfusion imaging in excluding PE in pregnancy. This study is doing exactly that.

Chapter 2: Goals and Objectives

2.1 To compare the efficiency of perfusion-only imaging for exclusion of pulmonary embolism in pregnant patients against a clinical outcome of any pulmonary

embolism which may have occurred during a period of 90 days post initial scan and initial visit.

2.2 To assess the diagnostic performance of perfusion-only imaging for the diagnosis of PE with emphasis on its negative predictive value for the exclusion of PE in pregnancy.

Chapter 3: Methods

3.1 Research Design

REB approval from TOH research ethics board was obtained prior to initiation of this retrospective cohort study. A comprehensive search was performed in the PACS, by using appropriate keywords, identifying pregnant patients who underwent V/Q study in the division of nuclear medicine at TOH. All pregnant patients suspected of having PE who underwent V/Q scan at TOH were included. The time interval for these patients was January 2004 until December 2015 (when the search was conducted).

A comprehensive list of patients who were captured by the search in the PACS was generated. Using patients' medical record numbers (MRNs), their perfusion scans were reviewed and assessed for any perfusion defects. The perfusion images were read by a resident (the writer) with two years of experience reading lung scans and the results were compared with the reports of V/Q scans which were made by the staff nuclear medicine specialists (with variable working experience). The reports were made at the time when the V/Q scans was performed. The perfusion-

only scans were read blindly to the ventilation images and a final diagnosis of "PE present", "PE absent" or "indeterminate study" were solely made based on the perfusion images, using the PISAPED criteria (table 1). The perfusion-only reader was not blinded to a recent chest X-rays, if there was one available or the patient's clinical information (available on the patient's requisition by the referring doctor or hospital electronic database vOASIS), in order to simulate the real practice. If a recent Chest X-Ray was performed, the findings were captured by the image reader. In those patients who did not have a normal lung scan, the follow-up clinical notes were reviewed up to 90-days post lung scan, in order to find out about the final diagnosis of the patient. For all patients with either normal or abnormal lung scans, if available, all the follow-up medical imaging related to PE were reviewed and the results were captured.

3.2 Study Period

All pregnant patients with suspected PE who were referred to the division of nuclear medicine at TOH for the assessment of PE and their images were available to us (in the PACS) were included. These patients were referred to the nuclear medicine department, in a period from January 2004 until December 2015 (when the patient search was conducted).

3.3 Study Center

The study setting included nuclear medicine departments at The Ottawa Hospital (both Civic and General campuses), in Ottawa, Ontario which is affiliated with the University of Ottawa.

3.4 Study Population

3.4.1 Inclusion Criteria

All the pregnant patients, at any stage of pregnancy, with or without classic PE symptoms such as shortness of breath and chest pain, who were referred for V/Q scan between January 2004 and December 2015 with images available on PACS, were included.

3.4.2 Exclusion Criteria

Images with artefactual findings or those with high levels of noise where an accurate interpretation would not be made were excluded. Patients with history of chronic PE were excluded. No exclusions were made based on recent chest X-ray findings, underlying lung parenchymal disease, anti- coagulation treatment or concurrent diagnosis of DVT.

3.5 Design of Study Database

A Microsoft Excel spreadsheet used to capture all the data pertinent to the patients as well as the interpretation of the perfusion scans. We housed the database on a central hospital based server at TOH, following REB guidelines.

3.6 Study Flow

A resident with two years of experience reading lung scans analyzed perfusion-only images using Hermes Workstation Software version 4.12, without correlation with ventilation scans. The Hermes program allows the interpreters to observe only the perfusion images. The resident was not blinded to a recent Chest X-ray or any clinical information if it was felt they should be reviewed before making the final diagnosis. If, rarely, instead of ventilation-perfusion scans, patients were only assessed by perfusion-only scans, then the perfusion-

only images were interpreted. The final interpretation of perfusion-only images in addition to the other pertinent information of the patients was then entered into the spreadsheet.

3.7 Image Interpretation

The well-known "PISAPED" criteria were used for the interpretation of our perfusion only images (22). (Table 1) A uniform distribution of radiotracer activity with no evidence of wedge shape defects was considered a normal examination and was reported as "PE absent". If single or multiple wedge- shaped perfusion defects were identified, the study was reported "PE present". If neither of the above conditions were met, the study was interpreted as "non-diagnostic/indeterminate".

3.8 Quality Assurance

A series of six images including anterior, posterior, right anterior oblique, right posterior oblique, left anterior oblique and left posterior oblique views for each patient were technically evaluated by the resident at the time of reading the scans. If low quality of the images interfered with an accurate interpretation, then those series of images would be excluded from our study. All other images with for which an accurate assessment could be made would be kept in the study.

3.9 Data Recorded

Demographic information of the patients including age and the term of pregnancy were captured in the spreadsheet. Additional information including the date of scan, the dosage of radiopharmaceuticals used, any technical issues or artifacts, the results of the reports of the V/Q scans, the results of perfusion only images, and finally the results of patient follow up including follow up imaging or clinical follow up were also captured. Initial interpretation of the perfusion-only images was done blindly with no knowledge of the results of the V/Q scans.

We didn't look for any clinical prediction data, because the well-known clinical predictor algorithm published by Dr. Wells has not been validated in the pregnant patients and therefore was not mentioned by the referring doctors in most cases.

3.10 Outcome Measures

The primary outcome of the present study was absence of PE in those with normal perfusion-only images, both at the time of initial presentation (index presentation) and also during a follow-up period of 90-days post index presentation. By doing this, the negative predictive value of the perfusion-only imaging was measured, among other test characteristics. Patients, who were PE free, therefore didn't receive any anti-coagulation treatment at the time of diagnosis and in the follow-up period. Exception applied to those patients who empirically received one or two doses of anti- coagulation when initially presented to the emergency department or the thrombosis unit, because some patients may end up receiving such doses of anti-coagulation even before undergoing lung scan or CTPA. Patients whose perfusion-only images were read as "PE present" or "non- diagnostic" were assessed clinically,

usually by thrombosis unit specialists, and based on the likelihood of PE, a course of action which typically included treatment or further imaging was taken. Our study also compared the negative predictive value of a normal perfusion-only scan with that of a normal V/Q scan to assess for consistency of the results.

3.11 Data Analysis

3.11.1 Descriptive Statistics

Analysis of the data was performed using SAS statistical program; version 9.2. When appropriate, descriptive statistics was used and statistical parameters such as mean with standard deviation or ranges were reported.

3.11.2 Reference Standard

The outcome data based on 90-day follow-up information was utilized as the reference standard. By comparing the results of perfusion-only images with those from the reference standard (90-day follow-up), multiple test parameters including true positive, true negative, false positive and false negative were measured. Using the above parameters, a two-by-two table, so called "contingency table" was generated (Table 3).

Table3. A two-by-two contingency table demonstrating perfusion-only scan results against 90-day follow-up outcomes

	90-days follow-up outcomes	
Perfusion only scan	Positive	Negative
Positive	True Positive	False Positive
Negative	False Negative	True Negative

3.11.3 Statistical Unit

The statistical unit in this study was the patient and not the perfusion defect and therefore all the parameters of diagnostic performance were measured on the basis of patient by patient.

3.11.4 Measures of Diagnostic Performance

Using the information in the contingency table shown above, the following diagnostic performance indices were calculated (23):

- ❖ Sensitivity
- ❖ Specificity
- ❖ Positive predictive value (PPV)
- ❖ Negative predictive value (NPV)
- ❖ Overall accuracy

Table4. The definition and formula for the above diagnostic performance indices

Index	Definition	Formula
Sensitivity	Ability to identify the presence of disease	TP/(TP+FN)
Specificity	Ability to identify the absence of disease	TN/(TN+FP)
Positive Predictive Value	Reliability of the positive results	TP/(TP+FP)
Negative Predictive Value	Reliability of the negative results	TN/(TN+FN)
Overall accuracy	Global reliability	(TP+TN)/(TP+TN+FP+FN)

3.11.5 Univariable Analysis

We used the limited number of predictive variables to experimentally run univariate analysis. For this purpose, we used chi square test or Fisher exact test when appropriate.

3.11.6 Sample Size Calculation

In this study, negative predictive value (NPP) is defined as: normal scans with subsequent negative 90-day clinical follow-up divided by all normal perfusion-only scans. To produce narrow confidence intervals around the NPP (primary outcome), all patients searchable in our database were included. We expected that at least 75% of scans will be normal (9). Therefore, a total of 300 normal scans (75% of 400 scans found in our initial search in the PACS) were assumed to be normal with no perfusion abnormalities. Assuming that failure rate of perfusion only imaging was 1%, using a sample size of 300 patients, the 95% confidence limits of the failure rate would be 0.003 and 0.029. For such calculation, as the standard Asymptotic (Wald) method does not produce meaningful estimation, given the product of “n” and “p” being very low, Wilson Score interval test was

utilized. (27) Assuming at lease a total of 300 scans will be normal, when Wilson Score interval test applied, the confidence limits of failure rate for different error rates and different confidence levels were estimated (Table 5).

Table5. Confidence limits of failure rate for different error rates at 95% and 99% confidence levels

Sample Size	Failure Rate	Confidence Level	95% Confidence Limits
300	1%	95%	0.3%-2.9%
300	2%	95%	0.9%-4.3%
300	3%	95%	1.6%-5.6%
300	1%	99%	0.3%-3.9%
300	2%	99%	0.7%-5.3%
300	3%	99%	1.3%-6.7%

3.11.7 Ethics

REB approval was obtained from TOH research ethics board prior to the initiation of this retrospective cohort study.

Chapter 4: Results

The study population consisted of 364 pregnant patients who were evaluated for PE at the Department of Nuclear Medicine at TOH during years 2004 to 2015. Of a total of 364 series of lung scans, V/Q scan was performed in 362 cases and perfusion-only scan was performed only in only two cases. Two series of lung scans were excluded as they were assessed for acute PE in the context of chronic PE.

Mean maternal age at the time of lung V/Q scan was 30.3 years-old (SD=5.8) ranging from 16 to 51 years-old. Of a total of 362 patients included in the final analysis of the data, 151 patients (41.8%) were under the age of 30, 182 patients (50.2%) were between 30 and 40 years old, and 29 patients (8%) were above 40 years old. When the distribution of final diagnosis of PE among different age groups was analyzed, it was noted that all the cases of PE were above the age of 40. Table 6 summarizes the rate of PE in different age groups. Similar findings were also reported in prior literature where most patients diagnosed with PE were over 35 years-old (41).

Table6. Distribution of final diagnosis of PE in different age groups

	Age groups		
Final diagnosis of PE	<30 year-old	30-40 year-old	>40 year-old
PE negative	151	182	14
PE positive	0	0	15

From a total of 362 lung perfusion scans, 316/362 (87.3%) scans interpreted as normal, 17/362 (4.7%) scans were interpreted as high probability of PE and 29/362 (8.0%) scans were interpreted as non-diagnostic. No scans were excluded due to technical failures. Six scans had artifacts that did not interfere with the interpretation of the perfusion images. A total of 15 patients (4.14%) were diagnosed with PE at the time of initial visit, with no additional diagnosis of PE during the three months follow- up period.

Information in regards with pregnancy stage was available only for 294 patients. 137 patients (46.8%) had presented in their 3rd trimester of their pregnancy (more than 26 weeks), 112 patients (38.4%) had presented in their 2nd trimester of their pregnancy (more than 14 weeks and less than or equal to 26 weeks) and finally, 45 patients (14.8%) had presented in their 1st trimester of their pregnancy (less than or equal to 14 weeks). When pregnancy stage compared against number of final diagnosis of PE, no statistically significant difference among the three groups noted (Chi-square: 5.453, degree of freedom: 2, P-value: 0.06). (Table 7)

Table7. Comparison between final diagnoses of PE against pregnancy terms

	Pregnancy term		
Final diagnosis of PE	1st trimester	2nd trimester	3rd trimester
PE negative	41	107	135
PE positive	4	5	2

Chest X-ray:

162 patients (44.1%) had a prior recent chest X ray, conducted within the last 24 hours of the lung scan, available in the PACS. 139/162 (85.8%) of these cases had a normal perfusion-only lung scan, of which 131/139 had a normal chest X-ray and only 8/139 cases had abnormal chest X-ray. 13/162 cases with chest X-ray had an indeterminate perfusion-only scan, of which 8/13 cases had normal chest X-ray, 1/13 patient had indeterminate chest X-ray and 4/13 cases had abnormal chest X-rays. Finally, 10/162 cases with accompanying chest X-ray were positive

for PE, who all (10/10) had normal chest X-rays.

Additionally, of 162 patients who had CXR, 85.8% had a negative perfusion scan. Of 200 patients with no CXR, 88.5% had a negative perfusion scan.

When Chi-Square applied, it was considered that it was unlikely that the distribution of negative perfusion scan differs between those with CXR and those without it (p value=0.4). Therefore, it is unlikely that presence of absence of an accompanying CXR had a major impact on the type of diagnosis was made on the perfusion only scans.

Table8. Perfusion scans interpretation versus chest X-Ray findings

	Chest X-Ray			
Perfusion scan interpretation	Normal	Indeterminate	Abnormal	Total
PE absent	131	0	8	139
Indeterminate	8	1	4	13
PE present	10	0	0	10
Total	149	1	12	162

Leg Doppler Ultrasound:

A sum of 208 patients (57.5%) had an accompanying ultrasound (to rule out DVT). Of these patients, 198 patients had a negative leg US and only 10 patients had a positive leg US. Of 208 patients with leg ultrasound, 175 patients were PE absent, 25 patients were indeterminate and 8 patients were PE positive. 8 out of 175 patients (4.5%) with normal perfusion-only lung scan had a positive leg US. All

these patients had chronic DVT and were on Anti-coagulation treatment even prior to the undergoing lung scans or had ultrasound findings suggestive of DVT. In those with indeterminate lung perfusion-only scans, none of them (0/25) had a positive leg US. Finally, of those with positive scans for PE, 25% (2/8) had a positive leg US and 75% (6/8) had a negative leg US (Table 9).

Table9. Perfusion scans interpretation versus leg ultrasound diagnosis

	Leg Ultrasound		
Perfusion scan interpretation	Negative for DVT	Positive for DVT	Total
PE absent	167	8	175
Indeterminate	25	0	25
PE present	6	2	8
Total	198	10	208

Follow-up Studies

Clinical and Imaging Follow-Up

Clinical follow up data for patients with normal perfusion-only imaging (100% of whom also had normal V/Q scans), were not captured. In fact, in most cases no clinical follow up was available, because in clinical practice, a normal lung scan excludes PE. However, for this group of patients (those with normal perfusion-only scans), we looked for any follow-up lung scintigraphy or CTPA. Except two cases, none of the patients in this group had a follow up lung scintigraphy or follow up CTPA examinations. Therefore, it was judged that these patients, indeed, did not have PE and therefore did not seek any subsequent medical

attention. The only two patients who were referred twice for lung scan during same pregnancy were found negative for PE on the subsequent examination.

High Probability Perfusion-Only Scans Cleared For PE on Follow-up

In three patients with high probability perfusion-only scans, pulmonary embolism was excluded:

1- One patient (with V/Q scan interpreted as indeterminate) had two negative follow-up leg ultrasounds and was later assessed by CTPA which was also negative for PE.
2- The second patient (with V/Q scan was interpreted as very low probability) and had two negative follow-up leg ultrasound was deemed clear for PE.
3- The third patient (with V/Q scan interpreted as indeterminate), who had a normal Chest X-ray and four negative follow-up leg ultrasounds, also was cleared for PE.

In all these three cases, patient deemed clear for PE and therefore was not treated with anticoagulation medications. This means that in perfusion-only imaging falsely categorized three normal individuals as high probability for PE (false positive).

Follow-Up Leg Doppler Ultrasound

A total of 25 patients with indeterminate lung perfusion-only scans had coexisting or follow-up leg ultrasounds. Of these, three patients had three negative follow-up leg ultrasounds, eleven had two negative follow-up leg ultrasounds and the rest

(eleven patients) had one negative follow-up leg ultrasound. In other words, all patients with indeterminate lung perfusion scan who were followed by leg ultrasound, were found negative for DVT.

Eight patients with high probability perfusion-only scans, has concurrent or follow up ultrasound. 1/8 patient (with indeterminate V/Q scan) had three negative follow-up leg ultrasounds hence cleared for PE. 5/8 patients (one with normal V/Q scan, one with indeterminate V/Q scan and three with high probability V/Q can) had undergone one follow-up ultrasound and cleared for PE. 2/8 patients (with high probability V/Q) had positive accompanying leg ultrasounds and were diagnosed with PE.

Perfusion-Only Scan

Follow-up clinical notes or follow-up imaging (if present) were reviewed for 46 of 362 patients, who had perfusion defects including indeterminate or high probability. In other 316 patients with normal perfusion scans (who all had normal V/Q scans), a diagnosis of PE was excluded. A final diagnosis of PE was made for a total of 15/362 (4.14%) patients based on the initial lung scintigraphy with clinical likelihood of PE. In 14/15 patients, lung perfusion-only examinations (as well as lung V/Q exam) were reported as high probability for PE. In 1/15 patient with a final diagnosis of PE, the lung perfusion-only examination was indeterminate (lung V/Q scan had high probability). This patient had a chest X-ray showing left basal atelectasis, had accompanying leg ultrasound showing slow blood flow in one leg

and no DVT in the other leg. Patient was adjudicated as having PE and was treated with anticoagulation. The 6 months follow up V/Q scan showed resolution of perfusion defects, in keeping with interval resolution of PE. (Table 10)

Table10. Perfusion scans interpretation versus final diagnosis of PE in 362 patients.

	Final Diagnosis		
Scan Category	PE present	PE absent	total
PE +	14	3	17
PE -	0	316	316
Indeterminate	1	28	29
Total	15	347	362

CT-Pulmonary Angiography

A sum of four patients who had either non-diagnostic (3/4) or high probability (1/4) perfusion-only scans had undergone follow up CTPA and all of them were negative for PE.

Diagnostic Accuracy Measurements

Diagnostic accuracy measurements were performed twice, first after deleting the non-diagnostic images and next, after including the non-diagnostic scans and considering them as positive for PE.

Stage I Analysis

After deleting the non-diagnostic studies, there were a total of 14 patients with a

final diagnosis of PE. None of the patients with normal perfusion-only examination were diagnosed with PE, giving a failure rate of 0%. The efficiency of perfusion-only imaging was therefore 81.0% (316/330). The sensitivity and specificity of perfusion- only imaging after excluding the non-diagnostic studies were 100% (100% - 100%) and 99.1% (98.0% - 100%), respectively. At this stage of data analysis, a negative predictive value (NPV) of 100% (CI: 100% - 100%) and a positive predictive value (PPV) of 82.4% (CI: 64.2% - 100%) were measured. (Table 11)

Table11. Diagnostic performance of perfusion-only scan at stage 1 of data analysis (Non-diagnostic scans were excluded)

	Number of patients	%
True Positive	14	4.2
False Positive	3	0.9
True Negative	316	94.9
False Negative	0	0
Accuracy	330 (accurately classified)	99.1

Table12. Diagnostic performance of perfusion only scans at stage 1 of data analysis.

	Estimate (%)	95% LCI (%)	95% UCI (%)
Sensitivity	100	100	100
specificity	99.10	98.00	100.00
PPV	82.40	64.20	100.00
NPV	100.00	100.00	100.00

Stage 2 Analysis

In the next stage of analysis of the data, the non-diagnostic studies were also included and diagnostic accuracy parameters were analyzed. A total of 15 patients had a final diagnosis of PE. None of the patients who had a normal perfusion-only examination were diagnosed with PE: failure rate: 0%. The efficiency of perfusion only imaging after including the non-diagnostic studies was therefore 81.0% (316/330), similar to stage 1. The sensitivity and specificity of perfusion-only imaging after including the non-diagnostic studies were 100% (100% to 100%) and 99.1% (88.1% to 94.1%), respectively. At this stage of data analysis, a negative predictive value of 100% (100% to 100%) and a positive predictive value of 32.6% (19.1% to 46.2%) were measured (Table 13).

Table13. Diagnostic performance of perfusion-only scan at stage 2 of data analysis

(Non-diagnostic scans were included)

	Number of Patients	%
True Positive	15	4.1
False Positive	31	8.6
True Negative	316	87.3
False Negative	0	0
Accuracy	331 (accurately classified)	91.4

Table14. Diagnostic performance of perfusion only scans at stage 2 of data analysis

(Non-diagnostic scans were included)

	Estimate (%)	95% LCI (%)	95% UCI (%)
Sensitivity	100.00	100.00	100.00
specificity	91.06	88.10	94.10
PPV	32.60	19.10	46.20
NPV	100.00	100.00	100.00

A total of 162 patients were evaluated by chest X-Ray at the time of assessment for PE. Of those, 149 patients had normal chest X-ray, one patient had an equivocal chest X-Ray findings and 12 patients had abnormal findings. Table 15 demonstrates the type of abnormal chest X-ray findings, in correlation with the perfusion-only and

V/Q scan interpretations.

Table15. Radiological findings in 12 abnormal chest X-Rays.

Chest X-ray findings	Perfusion-only interpretation	V/Q scan interpretation	Final Diagnosis
Ground glass, pneumonia	Indeterminate	Normal	No PE
lobar atelectasis	Normal	Normal	No PE
band-like sub-segmental atelectasis in right middle lobe	Normal	Normal	No PE
low lung volumes	Indeterminate	Indeterminate	No PE
bi-Basilar Atelectasis	Normal	Normal	No PE
questionable RML consolidation	Normal	Normal	No PE
bilateral lower lobes pneumonia	Indeterminate	Indeterminate/high	No PE
right lobe linear atelectasis	Normal	Normal	No PE
tiny pleural effusion-likely PE	Normal	Normal	No PE
interstitial pattern	Normal	Normal	No PE
Right lower lobe infiltration	Indeterminate	Indeterminate	No PE
left basal atelectasis	Indeterminate	High	PE

Reproducibility of Perfusion-Only Scans

There was 100% agreement between the results of perfusion-only examinations and V/Q scan reports when the perfusion-only scans were normal and demonstrated no perfusion defects. Of the 29 patients whose perfusion-only examinations were reported as indeterminate, the V/Q scan results for these 29 patients were as follows:

13 cases were reported as no evidence of PE, 12 cases were reported as indeterminate for PE, one case reported as borderline normal/indeterminate, two cases were reported as indeterminate/high probability and one case was reported as high probability. In our study, only two patients had a repeat lung scan and in both cases the scans were negative for pulmonary embolism.

Chapter5. Discussion:

The current study has demonstrated that perfusion-only lung scan, had a very high negative predictive value of 100% in pregnant patients who were assessed for PE in the setting of TOH. The perfusion-only lung imaging was 100% sensitive and 99.1% specific for the diagnosis of PE after exclusion of non-diagnostic images and 100% sensitive and 91% specific for PE when non-diagnostic images were included in the data analysis and considered as false positive. The perfusion-only lung scan had a 99.1% accuracy when non-diagnostic images were not considered and had a diagnostic accuracy of 91.4% after inclusion of non-diagnostic studies. Positive predictive value was 82.4% after including the non-diagnostic studies and it dropped to as low as 32.6% when non-diagnostic studies were included in the analysis of the data.

Perfusion-only scan has been used for the assessment of pulmonary embolism in pregnant patients in the past and presently in some centers. However, the available evidence for diagnostic accuracy of perfusion-only imaging in pregnancy appears insufficient. In early reports, it was shown that lung ventilation-perfusion scan has a high negative predictive value for ruling out PE in pregnant patients. Consequently, very few studies attempted to assess the accuracy of perfusion-only imaging in the workup of pregnant patients suspicious of having PE. These studies failed to employ a large pool of pregnant patients or to use the appropriate image interpretation criteria. The present study however, utilized a

large pool of pregnant patients suspected of having PE and used the well-known and the most relevant PISAPED criteria for reporting the perfusion-only imaging findings. The patient population employed in this study included the entire pregnant patients who were referred to the department of nuclear medicine at TOH in Ontario, whose lung scans were available to us in the PACS (in a time interval from 2004 to 2015). Therefore, no sampling or patient selection was conducted.

In the retrospective study of Scarsbrook et al. which included 94 pregnant patients suspected of having PE, 92% of the scans were reported normal, 7% non-diagnostic (low or intermediate probabilities) and 1% high probability. These measures for our study were 87.3%, 8% and 4.7% respectively. Both studies, therefore, demonstrated a high percentage of normal V/Q scans, even though they used different interpretation criteria (modified PIOPED II). Employing different interpretation criteria cannot play a role in interpretation of normal scans, as normal scans are called when there are no perfusion defects, irrespective of interpretation criteria being used. Scarsbrook et al. also showed that none of patients with normal or non-diagnostic lung perfusion scans were later diagnosed with PE or required anti-coagulation therapy, suggestive of a very high negative predictive value of normal perfusion-only scans. These results are also in keeping with the 100% negative predictive value measured by our study. Both studies also report similar numbers of non-diagnostic examinations; 7% on Scarsbrook study, vs. 8% on our examination.

Our study included patients from 2004 until 2015 (versus 2001-2005 in Scarsbrook et al. study), and therefore it maybe more reflective of the contemporary practice guidelines which recommends performing lung scans in the patients with no pulmonary conditions, and therefore it would be expected to have a lower rate of non-diagnostic examination in our study. Finally, the study reports a 3% incidence of PE in pregnant patients which is comparable to the rate of PE in our patient population (4.14%), yet higher in our study population. The minimal higher rate of PE in our study, even if considered real, could be due different patient characteristics, underlying individual, behavioral and/or societal risk factors. The above study, alike ours, was a retrospective study and subject to missing the information in regards with follow up lung scans. Although, missing patients on follow-up in our study is less likely, considering most patients should have been followed for their condition at TOH.

In a subsequent study of 99 consecutive pregnant patients with clinically suspected pulmonary embolism in 2010 by Shahir et al., a total of 96 patients had negative perfusion-only examinations, of which 63 (65.6%) had normal scans, 14 (14.5%) had very low probability scans and 19 (19.7%) had low probability scans. To interpret the results, modified PIOPED I criteria were used. Although the high number of normal scans reported by Shahir et al. is in keeping with the findings of our examination, an accurate comparison of the indeterminate and high results may not seem feasible, since two different interpretation criteria has been used. The modified PIOPED I interpretation criteria was developed based on the image

findings of both ventilation and perfusion images. A second consideration is that in Shahir et al. study, all "very low probability", "low probability" and "normal" exams were classified as normal exams. This is different from what was done in our examination, where study reported as normal only if there was no perfusion defects, otherwise studies reported as indeterminate or high probability. This is possibly why Shahir et al study has a very low rate of non-diagnostic examinations (3%) which is considerably lower than our study (8%). Overall, similar to our examination, Shahir et al. study showed 100% negative predictive value for a normal perfusion-only examination when comparisons were made to CTPA results and 99% negative predictive value when clinical follow-up results were used as the reference standard.

And finally, in terms of saving in the expenditure and resources and improving patient convenience, even though these were not our main objectives of this research project, out data shows that only a small fraction of all pregnant patients referred for lung scan require to come back the next day for the inconvenient ventilation examination. An exact proportion cannot be given, because it depends on what cases are referred by the clinicians based on clinical probability. For example, a patient with high clinical probability lung scan who also has high clinical probability for PE may not brought back to the hospital for ventilation examination, even though the perfusion images demonstrated abnormalities. However, we estimated that a proportion of 1/20 to 1/7 of the patients will be returned for ventilation examination.

5.1 Strengths and limitations of the study

This is the first study to validate perfusion-only imaging in a very large number of pregnant patients (362 pregnant patients), suspected of having PE visited at TOH. The large number of study subjects includes patients who were assessed at TOH over a period of approximately ten years. The study looked at the three month follow up document if available in our electronic database, to capture those with missed PE due to normal lung perfusion scans.

Although for the purpose of thesis a smaller size patient population could be evaluated, it was decided to include the entire patients available to us in order to produce higher levels of power and narrower degrees of confidence interval. Fortunately no scans had to be excluded due to technical failure including artefactual findings which by itself indicates good procedural skills of technologists at the Department of Nuclear Medicine. Only two patients were excluded from our study due to having chronic PE.

For interpretation of the perfusion only examinations, PISAPED criteria were used, which we think is the appropriate interpretation criteria when no ventilation imaging is available. We don't believe using PISAPED or PIOPED criteria produce different numbers of normal (or near normal) studies. However, given only one large segmental perfusion defect is required to call a high probability perfusion scan on PISAPED where as two large segmental mismatch

perfusion defects are required to call a high probability on PIOPED, PISAPED may be more sensitive in detecting PE as compared with PIOPED. As for the clinicians, a higher degree of sensitivity of in pregnant patients maybe of more interest, considering these patients are considered high risk.

Usually in similar studies, two image readers read the images independently. In the current examination, due to limited resources available for the conduct of this study, one image interpreter interpreted all the perfusion only lung scans and the results were compared against the reports were made by staff nuclear medicine specialist at the time of the conduct of the study. The nuclear physicians were of all seniority and experience levels, therefore enhancing external validity of this study.

The target population in this study was pregnant patients who were evaluated for PE at TOH. We included all patients with their lung scans available to us in our electronic databases, therefore no selection or sampling took place. Therefore, assuming no significant difference existed between patients who were managed at TOH during the past 10 years and those who were evaluated before or after this time interval, we can be assured that the current study is not subject to sample bias (28, 29, 30, 31).

Although it is unlikely that patients with persistent symptoms were not re-evaluated at TOH and were assessed in other hospitals or clinics other than TOH,

the possibility of lost to follow up bias cannot be entirely excluded, given that lung scan can be done in other centers/hospitals (32). Also a pregnant patient with "missed diagnosis" may not want to come back (understandably) to TOH follow up.

It is unclear if the current study is subject to disease spectrum bias. Disease spectrum bias is defined as a bias occurring when only cases within a limited range of the disease spectrum are included. This means that there may have been cases with sub segmental pulmonary embolism that were missed on the lung scan and never were diagnosed later. This could have falsely increased the negative predictive value of the test. On the other hand, the clinical importance of a sub-segmental pulmonary embolism is controversial and missing such small pulmonary embolism may not make a clinically important difference on the results of this study (33).

Other types of selection bias including referral bias, participation bias, image-based selection bias, self-selection bias and finally study examination bias are of not relevant to the conduct of our study and therefore are not discussed. (34, 35, 36, 37)

The reference standard used for the diagnosis of pulmonary embolism which was consisted as three months clinical follow up, although is the common practice in the diagnostic studies on pulmonary embolism, it could be subject to differential verification bias. Knowing the results of prior lung scan in a pregnant patient who

has similar symptoms weeks later, may not warrant a follow up lung scan. Therefore, differential verification that may exist depend on the index test (perfusion-only scans): those pregnant patients who had a normal lung scan may not have undergone repeat lung scans to rule our PE.

Additionally, for the above reasoning, follow-up bias (or medical surveillance bias), where subjects differentially undergo follow-up evaluations, may have occurred in the conduct of our study. Interestingly, screening study are notorious for this type of observation bias, where patients with positive results on the screening examinations undergo more frequent and rigorous follow-up assessments. On the other hand, those patients with negative screening studies would not undergo rigorous follow up assessments as such measures appear not necessary for these subjects. Differential follow-up measures for patients with positive and negative screening test results can produce bias in the conduct of the study by misclassifying individuals in the healthy or diseased categories. (38)

Diagnostic review bias defined as when the study test results affect or influence the way the final diagnosis will be established needs to be addressed. The diagnosis of PE is a combination of clinical history, physical examinations, chest X-Ray and medical imaging including lung perfusion scan or CT angiography. Although clinical suspicion plays a major role in the establishing the final diagnosis of PE in most individuals, in almost all cases, a lung scan or CT angiography is requested to help with the diagnosis. By default, a normal lung scan excludes PE, therefore almost

always a patient with normal lung scan is considered PE free, unless the clinical suspicion for the presence of PE is very high, prompting further investigations. Therefore, although it seems unlikely that a normal lung scan incorrectly excludes PE in a pregnant patient with low or very low clinical probability for PE, it may have such potential in those cases who considered clinically borderline for PE. Auspiciously, the three month follow up as the gold standard test provided us with an opportunity to establish the correct diagnosis in case an accurate diagnosis could not be made at the time of initial visit. (35)

Approximately 8% of the studies were reported as non-diagnostic. This is not unexpected, as some studies may don't fall in the categories of PE present or PE absence, as defined by PISAPED criteria. This is not because the study did not qualify a confident interpretation due to technical factors or presence of artifact.

When planning the study, it was decided that patients with prior history of PE be excluded from our study. This was because, a prior PE may not have completely resolved and produce perfusion defects on the consequent lung perfusion scan, differentiating an acute from a chronic process challenging. Fortunately, only two patients were excluded as a result of this exclusion criterion.

Chapter6. Conclusion

The present study aimed at assessing the negative predictive value (among other diagnostic accuracy measures) of perfusion-only imaging in a large group of

pregnant patients, suspected of having PE. Within the limitations of a retrospective research the most important of which being possible lost to follow-up cases, the results of the current study show that perfusion-only imaging has a very high negative predictive value for PE in pregnant population and therefore can exclude PE with a very high degree of confidence. A normal perfusion-only imaging is considered a scan with no perfusion defect. In 87.3% of perfusion-only scans of the pregnant patients, no such defects were identified. None of the patients with normal perfusion only scans were diagnosed later with PE, proving a negative predictive value of 100%. The very high negative predictive value shown on perfusion-only imaging was reproducible if perfusion only examinations were considered solely or in combination with ventilation images. Our study also demonstrated that only 17 patients (out of 362 patients) who were assessed for PE were diagnosed with PE, a prevalence of 4.6%.

Section 2:

A Proposal for a prospective study

Title:

Measurement of the diagnostic accuracy of perfusion-only lung scan in pregnant patients suspected of having pulmonary embolism; a Prospective Cohort Study

1. Background:

Pulmonary embolism is a medical condition that presents with a triad of shortness of breath, pleuritic chest pain and hemoptysis. Other symptoms include cough and tachycardia. If left untreated, PE could cause cor-pulmonale and circulatory collapse. When blood clots are lodged in the pulmonary arteries, patients become alkaloid with low PAO2 levels. Laboratory examination that could be helpful to make a diagnosis include assessment of D-Dimer, which is considered an excellent screening test but non-specific for pulmonary embolism. Assessment of D-Dimer in pregnancy is not a routine practice due to physiologic changes during pregnancy that may alter the normal values of D-Dimer (7).

Pulmonary embolism is considered a major cause of maternal mortality during pregnancy (3). Therefore, making an accurate diagnosis is critical to these patients. Ventilation/Perfusion lung scan has been playing a major role in the management of pulmonary embolism in general and in pregnancy patients in particular. Another diagnostic tool consideration is computed tomography pulmonary angiography (CTPA). The problem associated with CTPA is the risk of radiation to individuals. The risk is even more concerning in pregnant patients due to increase in the volume of breast tissue during pregnancy as a result of hormonal changes (13,14).

There was a dramatic increase in the usage of CTPA for the diagnosis of PE in the past decade. Several reasons are speculated for such expansion. The first and most important issue was probably the lack of understanding of the harms associated with CT scan to the breast tissue especially in young women and in particular in pregnancy. A second factor could be the convenience ordering a CTPA compared with the difficulty ordering a V/Q scan. A third reason could have been the clinicians' lack of fully understating V/Q scan interpretations (24).

CT scans are known to produce much more radiation compare to the conventional chest X-ray. Measurement of radiation exposure to the patients and especially to the pregnant patients' breast tissue is not an easy task. In fact, dose calculation is challenging mainly due to variability in radiation absorption from organ to organ and from patient to patient. Insertion of a radiation detector in each organ to measure radiation exposure is not practical either (14).

2. Statement of the Problem

In the first part of this thesis, we have retrospectively demonstrated that perfusion- only imaging has a very high negative predictive value of 100% for ruling out PE in pregnancy. 87.3% (316/362) of patients who were seen by thrombosis specialist or emergency doctor at TOH, had a normal lung scan, defined as absence of any defects on the lung perfusion-only studies. None of these patients were found to have a final diagnosis of PE on the follow-up, proving a negative predictive value of 100%, irrespective of including non-diagnostic examinations. These results are in accordance with the results of prior studies performed using perfusion-only lung scan for the exclusion of pulmonary embolism in pregnant patients (10, 11).

The results of our study are however subject to the limitations associated with the retrospective nature of our study. Some of these limitations include lack of a thorough screening procedure for enrolling the subjects, lack of a dependable follow-up system in place, lack of information about any prior anti-coagulation injections to the patients before lung scan and lack of homogeneity in image acquisition over the years using old and new machines. Additionally, in our retrospective study we used the perfusion images of ventilation perfusion scans which is technically different than perfusion-only lung scan. Therefore, a prospective cohort study is needed to systematically assess the diagnostic performance of perfusion-only imaging in pregnant patients. Such study would be

needed should a decision to switch from ventilation perfusion scan to perfusion-only scan be made in the future at TOH.

3. Goals and Objectives

2.1 The purpose of our study is to prospectively assess the accuracy of perfusion- only lung scintigraphy for the diagnosis of pulmonary embolism in pregnant patients.

2.2 To determine the inter-reader agreement of the lung perfusion-only scans.

2.3 To determine whether the accuracy of perfusion-only imaging lung scan varies with patients' clinical characteristics.

2.4 To identify the possible clinical variables associated with PE in pregnancy.

4. Research Methodology

4.1 Study Design

The proposed prospective study will be conducted within the current practice of PE workup at TOH. Ideally, it would be optimal to produce a diagnostic diagram guiding clinicians for patient selection and patient referral for lung scan. However, to ensure the applicability of the proposed protocol, it was decided not to propose a new diagnostic algorithm and instead follow the current evidenced-based practice guideless at TOH for patient referral and patient selection.

Our proposed study is a prospective cohort study. An application will be submitted to research ethics board at TOH before the initiation of the study. Consecutive

patients at TOH will be recruited by the thrombosis clinic doctors. All thrombosis doctors will be contacted by a nuclear medicine resident to evaluate their willingness to cooperate with this study. Those willing to participate will be contacted and explained the logistics of the study and the use of study forms and will be provided a written instruction on how to cooperate with this research project.

4.2 Study Population

The entrance criteria consist of pregnant women of any ages and ethnicity with any language who are suspicious of having PE and are referred to the department of nuclear medicine for lung scan. Normally, these patients will present to the ER or the thrombosis clinic with signs and symptoms of PE such as shortness of breath or chest pain and are considered for further assessment. Other patients may be referral from other medical practices to thrombosis medicine.

Only those patients will be entered into the study who have no history of pulmonary parenchymal disease, as these patients are not recommended to be assessed by lung scan. Patients will be consented to undergo perfusion-only lung scans and will have to agree to stay available to the research team in the three months window following the perfusion-only lung scan. Patients will be reached by phone, mail or email.

We would like to ensure that all patients can be assessed against reference

standard of 90-days follow-up, therefore it is necessary to assess all patients against the 90 days follow-up outcomes. Patients who don't agree with the terms of this study and therefore unwilling or unable to provide written informed consent, those for whom follow up is not feasible or have allergy to the radiopharmaceutical will not be entered. It is highly unlikely any patient will be excluded on this basis, as this is an extra care and normally all patients would welcome extra care and extra attention. However in such cases, patient's demographics will be captured (if consented) and compared against the rest of the patients.

If enrolled, the hospital medical records of the patients will be reviewed, information regarding maternal demographics, stage of the current pregnancy, initial symptoms, ongoing symptoms and the most responsible physician's clinical probability will be captured.

The results of any other tests previously done for the patients, such as D-Dimer, Leg Doppler Ultrasonography or CTPA will also be captured. When seeing the patients in the department of nuclear medicine for lung scan, the information on immediate medical management including administration of anti-coagulation therapy will be assessed and captured. Patients will be contacted by mail, phone or email to set up three months post lung perfusion-only scan follow-up visit. Extra follow-up if needed will be scheduled to capture information in regard with delivery and pregnancy outcomes. The three months follow up data will be captured by primary care doctors including the thrombosis specialists or emergency physicians and the

forms will be reviewed by nuclear medicine doctor or resident to make sure all the required information are captured.

4-3 Perfusion-only imaging

The radiopharmaceutical which is used for perfusion-only imaging is 99mTc-MAA. The usual adult dose for perfusion-only imaging is 1 mCi. After requesting patient to cough and take a few deep breaths, 1 mCi of MAA will be slowly administered intravenously over a period of 3-5 respiratory cycles. The imaging is conducted in a supine position, unless patient cannot tolerate, in that case the imaging could be performed in the sitting position. Although unlikely to encounter, a well flushed indwelling line will be used for injection in case IV injection was unsuccessful. Swan- Ganz catheter or indwelling line with filter cannot be used for this purpose. Then, planar (2D) imaging will be performed in the standard views including anterior, posterior, left anterior oblique, left posterior oblique, right anterior oblique and right posterior oblique. After images are processed by the nuclear medicine technologist, a nuclear physician specialist or resident will review the images to ensure the quality of imaging and rule out any artifacts that may interfere with a confident interpretation of the scans. Although based on the current guidelines a perfusion only imaging should be performed in those with normal chest X-ray, a chest X-ray will not be required in each patient to exclude underlying parenchymal disease. Although a chest X-ray could be performed in those patients who are suspicious of having pulmonary disease or those who have a defect on the perfusion only imaging and therefore a radiological correlation deemed necessary in

order to interpret the perfusion-only findings.

The perfusion-only images will be interpreted by two independent nuclear medicine specialist and where there is disagreement, the opinion of a third nuclear medicine specialist will be obtained. Hermes Solution work station will be used for reviewing the images. The PISAPED reporting guidelines will be used for the interpretation of the images, because this is the most well-known relevant criteria that utilized a large number of perfusion-only images for the diagnosis of PE. Based on PISAPED criteria a scan considered normal when there is no perfusion defect. A high probability scan on the other hand is defined as a segmental perfusion defect with normal chest X-ray results. The diagnostic outcomes of perfusion-only images therefore will be: PE present, PE absent and Non-diagnostic.

Regardless of the results of the perfusion-only scans, the patients will be referred back to their referring doctor for any other necessary testing. The results of the perfusion only images will be available to the referring physicians at the time of visit to guide subsequent management. The referring doctors will carry out any other diagnostic procedures at their own discretion, based on the hospital practice guidelines.

4.4 Definition and Source of Predictor Variable

Demographic and clinical variables will be collected using patient's clinical charts and interviewing the patients prior to the perfusion lung scans. The following patient's characteristics will be captured: age, previous diagnosis of venous

thromboembolism, unexplained sudden unset dyspnea, pain on inspiration, unexplained cough, signs and symptoms that suggest deep vein thrombosis, pulmonary embolism being considered the most likely diagnosis, tachycardia (heart rate more than 100 beats per minute), history of immobilization, history of recent surgery, history of prior deep vein thrombosis, history of prior pulmonary embolism, history of blood in sputum and finally, history of active malignancy. (22).

4.5 Definition and Sources of Outcome Variables

4.5.1 The primary outcomes of this study will include the conventional diagnostic accuracy measures (sensitivity, specificity, positive predictive value and negative predictive value).

4.5.2 False negative rate or the failure rate defined as proportion of patients who were adjudicated to have experienced PE during the three month follow up period, but had a negative (normal) lung perfusion-only scans.

4.5.3 Efficiency of lung perfusion-only scan defined as proportion of lung perfusion- only lung scans that will be interpreted as normal among all lung scans.

4.6 Reference Standard

The diagnostic strategy at The Ottawa Hospital is based on the current practice guidelines. This is usually a combination of estimated clinical probability, lung scans and lower extremities Doppler ultrasound. The proposed research protocol will use a composite reference standard of perfusion-only lung scans, leg ultrasonography and clinical probability assessment. In addition, patients will be followed up for three months and one-month post-partum if the date of delivery falls outside of the

three month follow up window. The follow up will be done by phone calls or hospital visits, whichever is more convenient for the patients and deemed more appropriate considering the patient's diagnosis at the time of initial visit. At the follow up phone calls or hospital visits, the occurrence of any potential or recurrent venous thromboembolic events and or complications associated with medical treatments such as hemorrhage with anticoagulant therapies will be documented. The patients will also be asked about the outcome of pregnancy and any maternal or neonatal complications related to the subsequent delivery. At the end, an independent adjudication committee will evaluate all the patients who were evaluated for PE and make a final diagnosis of PE or no PE. Please see table 16 for a detail description of the reference standard.

Table16. Composite reference standard

Pulmonary Embolism confirmed	Pulmonary Embolism refuted
Perfusion-only lung scan findings are in keeping with PE, in accordance with PISAPED criteria OR Lung perfusion only imaging was normal but patient had a venous thromboembolic event during three months of follow up.	Perfusion only lung scan demonstrated no finings of PE in accordance with PISAPED criteria and three months of follow up was uneventful.

Leg compression ultrasound shows proximal deep vein thrombosis in a patient with clinical symptoms and signs of PE who is considered high risk for PE.	Leg compression ultrasound shows no proximal deep vein thrombosis or no ultrasound was performed in a patient who has three months of uneventful follow up period.

4.7 Statistical Analysis

SAS program version 7 will be used for all statistical analysis of the data. The diagnostic accuracy parameters of perfusion only imaging will be calculated including sensitivity, specificity, positive predictive value and negative predictive value. The false negative results of perfusion-only lung scan as well as efficiency of lung perfusion-only scan for excluding PE will be measured. To calculate the 95% confidence interval for the frequency of PE in patients with positive or negative perfusion only lung scans, binomial distribution will be utilized. The 95% confidence interval of failure rate will also be measured. Univariate analysis using Chi square or Fisher exact test will be utilized to assess the association between clinical parameters and primary outcomes, when appropriate.

4.8 Sample Size Calculations

To calculate the required sample size for the proposed prospective cohort study, we concentrated on exclusion of PE by performing lung perfusion-only imaging reaching a minimum number of false negative rates also called missed cases. In section 1 of this monograph we demonstrated that lung perfusion-only imaging has 100% negative predictive value for exclusion of PE, with an exact confident interval of 98.8% to 100%. We selected the lower limit of confident interval of this

estimate (98.8%) for calculation of sample size. We used this estimate to calculate the number of subjects required for our prospective study. Using these parameters, the following formula was used to calculate the sample size at different levels of confidence

$$n = \frac{p_0 q_0 \left(z_{1-\alpha/2} + z_{1-\beta} \sqrt{\frac{p_1 q_1}{p_0 q_0}} \right)^2}{(p_1 - p_0)^2}$$

We accepted a power (1-β) of 0.8, a type 2 error of 0.2. We defined the null hypothesis as "p=90%" and the H_A hypothesis as "p>90%" and assuming that the true value (p_1) being 98.8%. Therefore, suppose $p_0 = 0.9$ and $p_1 = 0.988$, we used the above mentioned sample size formula to calculate the sample size required to reach different levels of p_1, as brought in the Table 16.

Table16. Sample size required to reach different levels of p_1

P_1	90%	95%	97.5%	98%
N	34	78	188	254

5. Clinical Significance

The results of this study could have a significant impact on the assessment of pregnant patients suspected of PE at TOH. Currently, lung scintigraphy for the assessment of PE in pregnant women includes both ventilation and perfusion scans. It is our hypothesis that in a majority of pregnant patients, a diagnosis of PE can be ruled out using only a perfusion-only study. If the results of proposed prospective study would be in agreement

with what was measured in section 1 of this monograph, the profusion-only method could be adopted at TOH as the standard of care for this particular purpose. Such practice changing study may have a significant impact on the management of PE through exposing patients and their fetuses to lower amounts of radiation and therefore enhancing the acceptability of the study by the patients among previously discussed benefits.

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