Use of imaging for investigation of suspected pulmonary embolism during pregnancy and the postpartum period

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Summary: Pulmonary embolism (PE) is recognized as a leading cause of maternal mortality in the developed world; however, it is a very difficult diagnosis to make on clinical grounds, and in most cases imaging is required. Pregnancy is a recognized risk factor for venous thromboembolism, and symptoms of normal pregnancy including shortness of breath, tachycardia and leg swelling are included in clinical tools for risk stratification for PE in the non-pregnant population. This results in a very low threshold for imaging, despite concerns regarding the risk of exposure to ionizing radiation both for the fetus and the maternal breast. We reviewed the results of all ventilation/perfusion scans and computed tomography pulmonary angiograms performed in pregnant women at a single institution to identify how many of these tests were positive for PE, and which clinical features may identify a low-risk group. A total of 386 scans were performed to investigate 375 episodes of suspected PE, representing 1.3–1.5% of pregnant women. Fifteen patients were diagnosed with PE, giving an incidence of one in 2000 maternities. The only statistically significant factors associated with PE were smoking or the presence of multiple risk factors. Clinical features of tachycardia and leg swelling did not provide significant diagnostic value; however, the absence of pleuritic chest pain had a negative predictive value of 97.8%. Arterial blood gas and D-dimer were statistically different between those with and without PE but not to a clinically useful degree. Currently available clinical and laboratory tools are not adequate to exclude a diagnosis of PE in a pregnant patient, thus imaging is justified to exclude PE. Further longitudinal studies to identify a low-risk group who do not require imaging is vital.

Keywords: pulmonary embolism, venous thromboembolism (VTE), pregnancy, risk factors, CT pulmonary angiogram (CTPA), ventilation/perfusion scan (VQ)

INTRODUCTION

Pulmonary embolism (PE) is recognized as a leading cause of maternal mortality in the developed world;^{1,2} however, it is a difficult diagnosis to confirm, and particularly challenging to exclude, on clinical grounds. Clinical features such as leg swelling, tachycardia and pleuritic chest pain have shown poor discriminative value,³ presenting a greater challenge in the pregnant population where dyspnoea and leg swelling occur frequently. Widely used algorithms for risk stratification, such as the Wells Score,⁴ do not include pregnancy as a risk factor, nor have they been validated in the pregnant population. Risk factors for thrombosis including inherited thrombophilias, immobilization, surgery, obesity and smoking have a multiplicative effect with the procoagulant effects of pregnancy, potentially increasing risk of thrombosis up to 100× population risk.^{5,6} Investigations that can be used to help determine the risk for PE include the D-dimer, arterial blood gas (ABG) and ultrasound scan (USS) of the lower limbs; however, overall these have decreased diagnostic utility in pregnancy. D-dimer increases progressively over the course of pregnancy⁷ and cut-offs that provide adequate negative predictive value in

this population are not well defined. The Alveolar-arterial (A-a) gradient is normal on blood gases in up to 6% of non-pregnant patients with PE,^{8,9} and this may be as high as 58% in pregnancy.¹⁰ Similarly, USS has a limited negative predictive value as pelvic thrombus is more common in pregnancy and not often seen on USS of the lower limbs.¹¹ The low discriminative value of both clinical and laboratory diagnostic measures means that imaging is often required in pregnancy.

Nuclear medicine lung scanning compares ventilation to perfusion and may be limited to perfusion only scanning when the perfusion study is normal. The total radiation exposure is low, 0.8 mSv fetal dose.¹² The use of this modality is potentially limited by non-diagnostic scans of up to 40% for planar imaging^{11,13} and further imaging may be required to exclude PE. Computed tomography pulmonary angiogram (CTPA) was previously a second-line study in the investigation of suspected PE in pregnancy, and the expert opinion of two-thirds of Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) investigators recommended ventilation/perfusion (VQ).¹⁴ This difference is less pronounced now with the increased use of the more sensitive multidetector CT units, the sensitivity and specificity are now over 90%.^{15,16} There are concerns regarding the high dose of ionizing radiation (50–80 mSv with 64 slice multidetector CTPA versus 0.28–0.9 mSv with VQ lung scanning) to the maternal breast, predominantly

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related to the younger age of the women, and theoretical concerns regarding the risk of carcinogenesis due to the presence of proliferating breast tissue.^{17,18} The use of breast shields containing a bismuth compound purport to reduce the breast dose by up to 40% without reducing the quality of multidetector CT images;¹⁹ however, these shields are not yet widely available. In contrast to the maternal breast exposure risks, fetal radiation exposure with CTPA and abdominal shielding is low (0.03–0.13 mSv), although there are theoretical risks to the developing thyroid from the iodinated contrast load,^{11,16} which have not been borne out in a recent study of over 300 neonates.²⁰

We undertook an audit of all VQ and CTPA performed in women during pregnancy and the postpartum period to assess the utilization of imaging at our institution, and with the aim of identifying a low-risk group who may not require imaging.

METHODS

A retrospective chart audit was done of all VQ and CTPA scans performed on women who were pregnant or within three months postpartum at a single institution over the period from January 2002 to July 2008. All VQ and CTPA scans performed on women born between 1960 and 1990 were identified from the medical imaging database. Charts were requested for those patients where the report included the following words or abbreviations: pregnant, gestation (Kx), postpartum, partum, caesarian, lower uterine segment caesarian section (LUSCS), lower segment caesarian section (LSCS), or where there had been a recent pelvic USS, elevated serum/urine bHCG, admission to birth suite or admission under an obstetrician. Charts were reviewed for women up to three months postpartum in order to include both the highest risk period of six weeks postpartum, as well as recognizing that the risk of thromboembolism is increased in the three months after an event, allowing capture of any initially false-negative scans on re-presentation. It is recognized that this may have diluted the number of positive scans postpartum. Observations were taken from the initial presentation to the emergency department or outpatient clinic, and for inpatients were as documented by the reviewing medical officer at the time the decision was made to image the patient. A scan was determined to be non-diagnostic if stated in the initial report, for nuclear medicine scans reported as moderate probability, or if further chest imaging was carried out to exclude PE.

A α -gradient was calculated on mdcalc online and *P* values were calculated using STATA 10.0.

VQ lung scanning

All lung scanning was performed with the ventilation of 40 MBq of Technegas, and perfusion of 185 MBq 99mTc-macroaggregated albumin (Pulmolite; CIS-US, Inc; Bedford, MA, USA). A 0.5 VQ refers to reduced 99mTc macroaggregated albumin perfusion dose to approximately 100–110 MBq. VQ scans were acquired on gamma cameras (Siemens Healthcare; Knoxville, TN, USA) using low-energy low-resolution collimators on a 99mTc photopeak of 140 keV. Planar ventilation images were acquired for 200,000 counts or 300 seconds, and perfusion images acquired up to 500,000 counts. Views acquired of the chest for both phases included anterior, posterior, anterior and posterior oblique, which is from left and right.

All reporting was according to the PIOPED II criteria,²¹ which in short states that two segments of mismatched perfusion defect or equivalent are required to diagnose the presence of PE. Low probability or normal has less than 25% of a segment showing a mismatched perfusion defect and were considered negative if stated in the reports reviewed. Intermediate or inconclusive is between 25% of a segment to two segments of mismatched perfusion defects and were considered non-diagnostic when in report.

Computed tomography pulmonary angiogram

At least a 16-row multidetector CT scanner was used. The contrast (120 mL of iomeprol 300) was injected through intravenous at a rate of 3.5 mL/second. The scanners operated with 16 × 0.75 mm collimation at 0.9 pitch and 0.5 second rotation, and time and exposure factors were of 120 kVp and 230 mA, respectively. Dose modulation and automated bolus tracking software were employed on all scanners. Field of view included from 1 cm above the aortic arch to the diaphragm.

A positive study was identified when a CTPA showed an intraluminal filling defect within the pulmonary arteries. The capacity of scanners allows identification of up to fourth-order bifurcation of vessels with diagnostic certainty. If technical factors such as poor bolus tracking or patient movement compromised the image, then the scan was reported as inconclusive.

RESULTS

Over the 6.5 years of the review, 386 scans were performed to investigate 375 episodes of suspected PE. At an annual maternity rate of 4000–4500, this represents 1.3–1.5% of pregnant women. This included 326 nuclear medicine scans and 60 CTPA (Table 1).

Fifteen patients were diagnosed with PE, of which seven were antepartum and eight postpartum (6 of which occurred in the first 2 weeks, 1 in the 3rd week and 1 at 8 weeks postpartum), giving an incidence of approximately one in 2000 maternities. During the period studied, there were no deaths from PE at our hospital. The non-diagnostic rate for CTPA was 11.1% antepartum and 7.1% postpartum. In contrast, the non-diagnostic rate for ventilation/perfusion (VQ) was 1.3% antepartum and 1% postpartum. There were no non-diagnostic half-dose VQ scans and for perfusion only imaging the non-diagnostic rate was higher (Table 2), although still lower than reported rates.

There were no significant differences in age or body mass index of those with and without PE. Traditional risk factors were assessed, with the only statistically significant factors associated with PE being smoking or the presence of multiple risk factors (Table 3).

Clinical features of chest pain, tachycardia and leg swelling did not provide significant diagnostic value (Table 4). Chest

Table 1 Investigations for suspected PE

	Antepartum	Postpartum	Total
VQ	73	101	174
0.5 VQ	108	5	113
Perfusion only	30	1	31
0.5 perf only	8	0	8
CTPA	18	42	60

VQ = ventilation/perfusion; CTPA = computed tomography pulmonary angiogram

Table 2 Non-diagnostic rate for imaging

	Antepartum (%)	Postpartum (%)	Total (%)
VQ	1/73(1.3)	1/101 (1.0)	1.1
0.5 VQ	0/108 (0)	1/5 (20)	0.9
Perfusion only	1/30 (3.3)	0/1 (–)	3.2
0.5 perf only	1/8 (12.5)	0/0 (–)	12.5
CTPA	2/18(11.1)	3/42 (7.1)	8.3

VQ = ventilation/perfusion; CTPA = computed tomography pulmonary angiogram

Table 3 Risk factors for PE

Risk factor	No PE	PE	P value
Past history of PE	5.1%	6.6%	0.79
Family history of PE	8.6%	14.3%	0.47
Smoking	23.4%	53.9%	0.012
Immobilization	24.2%	26.7%	0.35
Surgery	8.8%	0%	0.23
CS (postpartum PE)	56.6%	75%	0.31
Thrombophilia	24.6%	33.3%	0.53
>1 risk factor	20.5%	46.7%	0.016

PE = pulmonary embolism; CS = caesarian section

Table 4 Clinical features

Clinical feature	PE (%)	No PE (%)	P value
Pleuritic chest pain	10/15(67)	140/365 (38)	0.0279
Dyspnoea	10/15 (67)	232/360 (64)	0.8602
Calf swelling	2/15 (13)	52/365 (14)	0.9203
Chest signs	8/15 (52)	80/343 (23)	0.008
Heart rate >100	7/15 (46.7)	121/355 (34.1)	0.3156
Oxygen saturation ≥98%	8/14 (57.1)	215/308 (69.8)	0.3154
BMI (mean)	27.52	28.76	0.64

PE = pulmonary embolism; BMI = body mass index

signs, including localized tenderness, rubs, wheeze or decreased air entry, were significantly more common in those with a PE (52% versus 23%, $P = 0.008$), although this has limited clinical utility for exclusion of PE. The rate of pleuritic chest pain was higher in those with PE (67% versus 38% $P = 0.027$), thus in our population the presence of pleuritic chest pain has a positive predictive value of only 6.6%, although the absence of pleuritic chest pain has a negative predictive value of 97.8% (95% confidence interval [CI] 94.7–99.2%).

The supplementary investigations of ABG and D-dimer were statistically different between those with and without PE but not to a clinically useful degree. ABGs were performed in a third of patients (127/375). The mean A-a gradient was 32.65 in those with PE and 22.49 in those without ($P = 0.40$); however, for A-a gradient <12 the rate was 17% (PE) versus 41.8% (no PE) ($P = 0.64$). D-dimer was also performed only in one-third of cases (127/375), and was statistically different for the mean (1.89 PE versus 0.62 no PE, $P = 0.018$); however, only 1.6% of those without PE (2/123) had D-dimer <0.15, the diagnostic level used for a negative predictive value of 99% at our institution.

DISCUSSION

PE is among the most feared complications of pregnancy. PE represents 20% of maternal mortality; however, the absolute incidence of PE is low at <1:1000, and that of fatal PE is 1.94/100,000.¹ In our institution, imaging is undertaken for as

many as one in 70 women during pregnancy, which reflects the degree of concern surrounding this complication, and the very limited capacity to exclude the diagnosis on clinical grounds. Most algorithms for the investigation of suspected PE focus on risk stratification as an adjunct to the interpretation of VQ results. Given that the risk of PE in pregnancy and the postpartum is 5–100× population risk,^{5,22} pregnant women are by definition moderate to high risk, regardless of their clinical picture. Certainly, in our population the clinical features did not reliably discriminate between those with and without PE, although it is well to be reminded how poorly discriminatory these features are even in the non-pregnant population.³ Of note, tachycardia (HR > 100) was more frequent in our population, but otherwise rates of leg swelling, chest pain and chest signs were similar to those in the non-pregnant population. While the rate of pleuritic chest pain is higher in those with PE (67 versus 38%), in our population the presence of pleuritic chest pain has a positive predictive value of only 6.6%, although the absence of pleuritic chest pain has a negative predictive value of 97.8% (5/230 patients, 95% CI 94.7–99.2%).

The only significant pre-existing risk factors identified were smoking, or the presence of multiple risk factors; however, pregnancy-specific risk factors such as preeclampsia, multiple pregnancy and parity were not assessed and it is acknowledged that this is a weakness of this study.

Supplementary investigations for PE ideally have a strong negative predictive value, in order to allow a reduced rate of imaging. In our study, this is true for D-dimer, as none of the patients with PE had D-dimer <0.15; however, only 1.6% of those without PE had D-dimer <0.15. The measurement of D-dimer is controversial and recommendations are confusing.^{7,12,15,16} An important caveat is that negative D-dimer in the setting of a low clinical probability^{8,23} has excellent negative predictive value, and as mentioned above, pregnant women are by definition not low risk, as highlighted by a recent case report²⁴ of a pregnant woman with multiple PEs and serially negative D-dimer. One concerning aspect of the use of D-dimer in pregnancy is that the elevation may be interpreted as suggestive of venous thromboembolism (VTE), rather than a normal finding in pregnancy, thus D-dimer has not only a very low yield for the exclusion of VTE but potential to increase the rates of imaging.

ABGs were performed in only a small subset of patients in this study. In this series, the A-a gradient was normal in 1/5 (20%) patients with PE who were tested. This supports previous statements that ABG cannot be advocated as an adequate test to exclude PE.⁹ The USS of the lower limbs was also performed in only 15–20% of cases, although this sample is biased by the method of case selection.

The rate of non-diagnostic CTPA was 8.3% overall, which is consistent with reported rates.²⁵ The non-diagnostic rate for nuclear medicine scans was very low. This may reflect the low rates of respiratory co-morbidity in this group, or may represent the redirection, or false application of this group to a low-probability result. It must be noted that in Australia the ventilation medium used is technegas. This agent is preferred for the determination of ventilation defects when compared with agents used in the USA such as 133Xenon and Tc99mDTPA, which rapidly wash out of the lungs. Technegas is inhaled and stays in the lung for a number of hours, enabling more prolonged imaging and single photon emission computed tomography (SPECT). This may have been a factor reducing the non-diagnostic rate when compared with the predominant US literature. It is reported in the literature that planar VQ lung

scanning has a reduced non-diagnostic rate in candidates with a normal chest X-ray.²⁶ Clinicians generally showed an awareness of concerns related to maternal breast radiation from CTPA scanning and where possible VQ imaging was selected, and in many cases low dose or perfusion-only imaging was used. The non-diagnostic rate for nuclear medicine scanning was low, supporting its use as a first-line investigation²⁷ subject to local availability and experience.

The non-diagnostic rates for perfusion only studies were high, although the numbers were small. In the event of a non-normal perfusion study requiring a ventilation study to be performed, it takes 24 hours for the perfusion tracer to decay. In this situation, the treating physicians sought a more rapid alternative study, namely CTPA. This study was limited to planar VQ scanning, which at the time of the study investigation was the main modality available. The most recent imaging modality for VQ scanning is VQ SPECT, which offers the advantages of three-dimensional imaging, and triangulation of lung segments. This has led to a large increase in both the sensitivity and particularly specificity of pulmonary embolus detection to rates comparable with CTPA (97% and 91%, respectively^{28,29}) and as the dose of radiopharmaceutical is unchanged the radiation dose is the same as for planar VQ scanning. Imaging time is reportedly unchanged with ventilation and perfusion SPECT taking up to 25 minutes in total.³⁰

The main strength of this study is the large numbers, and as it was performed at a tertiary centre with a large catchment area there is a low likelihood of having missed subsequent thromboembolic events. The weaknesses include the retrospective nature of audit, as the approach to investigation is not consistent across the institution and therefore not all data were available for every patient. The overall incidence of PE may be under-reported as the search method would not include those patients imaged at another site prior to transfer. As mentioned, data were not collected on pregnancy-specific risk factors including preeclampsia, diabetes, parity or multiple gestation, which may have helped to better identify a high-risk group, although is perhaps less important in identifying a low-risk group with the aim of reducing the need for imaging.

CONCLUSIONS

Currently available clinical and laboratory tools are not adequate to exclude a diagnosis of PE in a pregnant patient. Determination of clinical suspicion of PE is challenging and at this stage imaging is justified to exclude PE. The small potential risk associated with a low-dose radiation must be balanced against the risk of morbidity and mortality from undiagnosed PE. Further longitudinal studies to identify a low-risk group who do not require imaging are vital.

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