Diagnostic imaging to investigate pulmonary embolism in pregnancy using CT-Pulmonary angiography versus perfusion scan

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Background: Pulmonary embolism (PE) is one of the major causes of maternal mortality; however, its diagnosis based on clinical presentation is a significant challenge; therefore, imaging is required. This study aims to determine the nondiagnostic rate of PE in pregnant women who initially undergone computed tomographic pulmonary angiography (CTPA) or perfusion scan. **Materials and Methods:** In this cross-sectional study, all pregnant or 6-week postpartum women with clinical suspicion of PE were evaluated and underwent CTPA or perfusion scan between March 2017 and June 2019. The nondiagnostic rate of each method was defined as the outcome of this study. **Results:** One hundred and eighty-two women with a clinical suspicion of PE were included, among which the initial imaging method was CTPA in 122 (67.03%) and perfusion scan in 60 (32.97%) women. The nondiagnostic imaging for CTPA was significantly lower than the perfusion scan (9 cases (7.4%) versus 25 cases (41.7%), respectively). Logistic regression assessment revealed a statistical outcome by controlling the confounders including gestational trimester at diagnosis, hypertension, ejection fraction, and tachycardia (odds ratio 15.911, 95% confidence interval: 5.177–48.897, $P < 0.001$). **Conclusion:** Based on the current study, CTPA is superior to perfusion scans to diagnose PE among pregnant or postpartum women with normal chest X-ray suspicion for PE.

Keywords: CT pulmonary angiography, perfusion scan, pregnancy, pulmonary embolism

INTRODUCTION

Pulmonary embolism (PE) is one of the major causes of maternal mortality in developed countries. Surfing the literature has represented that 1.72 cases per 1000 deliveries have been diagnosed with PE, and mortality was one death in every 100,000 deliveries.[1,2]

PE's clinical diagnosis is a significant challenge due to the varieties of physical manifestations compatible with PE such as coughing, dyspnea, tachycardia, and calf swelling. This challenge gets more complex during pregnancy, as the risk of PE increases in this period, and also, there are significant limitations for imaging due to potential harm to the fetus.[3] On the other hand, anticoagulant medications should be initiated as soon as possible following PE diagnosis to prevent further complications. The matter about anticoagulant therapy is the increase in bleeding risk and their potential teratogenicity for the fetus.[4,5]

Ventilation-perfusion scan (V/Q) and computed tomographic pulmonary angiography (CTPA) are the primary means for definite PE diagnosis. Therefore, due to both modalities' radiation, a risk assessment is required to find the benefits versus harms of imaging for both mother and fetus.[6]

The prospective studies in the literature provided level I evidence in favor of CTPA for PE diagnosis compared

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with perfusion-ventilation scans, but pregnant women were excluded from the trials.[7] With these high-level data, some expert radiologists suggested CTPA as the preferred imaging for confirmation of PE diagnosis in pregnant women. However, physiologic changes in pregnancy, such as increased cardiac output, changes in plasma volume, and intravascular fluid distribution alterations might affect the performance and interpretation of CTPA in this population.[8] Therefore, some of the scientists preferred the ventilation-perfusion scan over CTPA.[9]

By developing multidetector computed tomography, the sensitivity and specificity of this new modality have promoted up to 90%, which increased the tendencies toward CTPA.[10] However, to the best of our knowledge, limited studies have evaluated values of CTPA versus perfusion scan for PE diagnosis in pregnant women and present a practical guideline to interpret and use each of the modalities rather than the other one.[6,11] The current study aims to determine the proper diagnostic imaging modality considering the nondiagnostic rate of CTPA versus perfusion scan for pregnant women suspicion for PE clinically.

MATERIALS AND METHODS

Study design and participants
In the current cross-sectional study, 182 pregnant or 6-week postpartum women undergone CTPA or perfusion scan were evaluated. The study was conducted on women suspicion for PE based on the clinical presentations that referred to Alzahra Hospital, the major tertiary referral center affiliated at Isfahan University of Medical Sciences from March 2017 to June 2019.

The study protocol which met the Helsinki declaration criteria was approved by the Regional Ethics Committee of Isfahan University of Medical Sciences with code number IR.MUI.MED.REC.1397.305. The study's principles were explained to the patients; they were reassured about their information confidentiality and signed written consent.

The pregnant or 6-week postpartum women who presented signs/symptoms of PE and their medical records for CTPA or perfusion were present in the hospital archives were included in the study. The type of modality for making PE diagnosis was selected by the pulmonologist responsible for each patient. The internal medicine specialist responsible for the study referred to the existing medical records of PE-suspected pregnant females and gathered the required information and imaging.

Anticoagulant-treated women before imaging or those with specific hallmarks in their X-ray, implying other pulmonary pathologies than PE, were excluded from the study.

The study population was included through convenience sampling; thus, those who met the criteria for participation in this study were included in the study.

Census method was used to include the studied population; therefore, all of the existing medical records that met the inclusion criteria were included in the study through convenience sampling.

Imaging modalities
The patients were classified into two groups; the first group who had undergone CTPA and the second group who had undergone a perfusion scan to diagnose PE. The selected modalities were derived from the medical records in the hospital's archives.

Both radiologic imaging methods were performed in standard protocols.

Computed tomographic pulmonary angiography
CTPA was performed by a 64-MDCT scanner using Light Speed VCT SYS, model Ge64 device (General Electric, Wisconsin), when the patient was supine positioned, arms were suspended above the head, and while holding the breath. The derived image of the CTPA area extended from the lung apices to the diaphragm muscle.

For intravenous contrast enhancement, 10 ml of bolus normal saline was primarily pushed through the intravenous cannula to reassure the intravenous pathway's efficiency. After that, 50 cc of iodinated contrast medium (Visipaque 320 mg/dL) was given at 4.5 mL per second speed by at least 18G intravenous cannula in the antecubital vein by 30 ml of normal saline pushing in that root.

Images were reconstructed in the axial plane with 0.6 mm intervals. Diagnosis of PE was confirmed by observing filling defect in the pulmonary arteries and its branches, which were subjectively graded in 5 scores based on the enhancement of pulmonary artery trunk, main pulmonary arteries, lobar, segmental, and subsegmental branches in order of 1–5.

CTPA images compatibility with PE were reported by an experienced radiologist who was blinded to the patients' medication and signs/symptoms.

Perfusion scans
Perfusion scans were done by administration of 2.0–4.0 MCi technetium-99 m macroaggregated albumin. Therefore, technetium-99 m macroaggregated albumin was injected through the antecubital vein. The mismatches between the chest X-ray and perfusion phases were recorded using a gamma camera.

The images were interpreted by an expert radiologist blinded to the medication and introductory presentations of the patients. Modified Prospective Investigation of PE Diagnosis II criteria were utilized to report the images in three categories: positive, negative, and nondiagnostic.[12]

Outcomes

The obtained data of this study included demographic information (age, twin pregnancy, and phase of pregnancy), presence of hypertensive disorder (chronic hypertension and preeclampsia), the symptoms/signs compatible with PE (calf swelling, dyspnea, coughing, pleuritic chest pain, hemoptysis, tachycardia, hypotension, and abnormal electrocardiography), abnormal serum levels of d-dimer (above 500 units were defined as abnormal), oxygen saturation at admission derived by pulse-oximetry, and left ventricular ejection fraction assessed through echocardiography performed at the time admission.

The status of PE diagnosis based on imaging was recorded as diagnostic and nondiagnostic. In this term, the reports of perfusion scans were presented as positive, negative, and nondiagnostic. Therefore, those with positive/negative reports for PE were included in the diagnostic group for perfusion scans and nondiagnostic reports in the latter group.

In the group undergoing CTPA, poor enhancement view up to segmental branches of pulmonary arteries was determined as nondiagnostic; otherwise, the patients were entered into the diagnostic group.

Statistical analysis

Data were analyzed with Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) software. Continuous and categorical variables were presented as mean ± standard deviation and frequency (percentage), respectively. The normality of continuous data was evaluated using the Kolmogorov–Smirnov test and the Q-Q plot. Continuous variables were compared between diagnostic and nondiagnostic imaging using independent samples *t*-test and categorical variables using Chi-square or Fisher's exact tests. Crude and multivariable binary logistic regression were used for measuring the odds of nondiagnostic PE by perfusion scan compared to computed tomography pulmonary angiography, and results have been presented as odds ratio (OR) and 95% confidence interval (CI) for OR. The binary logistic regression measurement was primarily performed in an unadjusted form and then, by adjustment for the probable confounding variables, including gestational trimester at diagnosis, hypertension, ejection fraction, and tachycardia. $P < 0.05$ was considered statistically significant.

RESULTS

The comparison of the patients' characteristics based on imaging modality

In this study, 182 women suspicion for PE were evaluated, among which the diagnosis of PE was confirmed for 13 (7.1%) ones by diagnostic imaging. One hundred and twenty-two (67.03%) cases underwent CTPA, and perfusion scan was performed for the latter sixty ones (32.97%). The patients' most common complaint was dyspnea (89%) and tachycardia (38.4%), respectively. The study's two groups were similar in terms of age, twin pregnancy, hypertensive disorders, clinical signs/symptoms for PE, phase of pregnancy, serum levels of d-dimer, left ventricular ejection fraction, and oxygen saturation ($P > 0.05$). Detailed information is demonstrated in Table 1.

The comparison of the patients based on diagnostic versus nondiagnostic imaging

Eleven cases (9.01%) in the CTPA group and two (3.33%) in the perfusion scan group were diagnosed as PE.

In the CTPA group, nine cases (7.4%) did not have judgmental contrast enhancement from lobar and below pulmonary artery segments; thus, they were classified as nondiagnostic, and the other cases in CTPA consisted of nine patients (7.4%) with enhancement to the end of the segmental branches and 104 cases (85.5%) to the subsegmental branches. Reviewing of perfusion scans was negative for PE in 33 cases (55%), positive for PE in 2 cases (3.3%), and nondiagnostic for 25 (41.7%) patients.

The comparison of the patients with diagnostic versus nondiagnostic imaging reports revealed insignificant differences in terms of demographic, signs/symptoms, and phase of pregnancy and clinical evaluations ($P > 0.05$) presented in Table 2.

The logistic regression assessment revealed 8.96 times increased probability of nondiagnostic outcomes for perfusion scans than CTPA (95% CI: 3.829–21.001, $P < 0.001$) in an unadjusted model. According to the requirement of matching the nondiagnostic rate of each imaging modality, variables with $P \leq 0.2$, including gestational age, hypertension, ejection fraction, and tachycardia, were adjusted. By the adjustments for the gestational trimester at diagnosis, hypertension, ejection fraction, and tachycardia, this probability increased to 15.911 (95% CI: 5.177–48.897, $P < 0.001$). Detailed information is presented in Table 3.

Thirteen patients were diagnosed with PE, among whom 11 patients were diagnosed by CTPA and two cases by perfusion scan.

Table 1: The comparison of the clinical and demographic characteristics of women undergone computed tomography pulmonary angiography versus perfusion scan

Variables	Perfusion scan (*n*=60), *n* (%)	CTPA (*n*=122), *n* (%)	*P*
Age (years)	30.41±5.41	30.09±6.56	0.722*
Twin pregnancy	3 (5)	3 (2.5)	0.310**
Hypertensive disorders			
Chronic hypertension	5 (8.3)	10 (8.2)	0.590**
Preeclampsia	1 (1.7)	6 (4.9)	0.265**
Clinical signs/symptoms			
Calf swelling	0	6 (4.9)	0.087**
Dyspnea	56 (96.7)	106 (96.7)	0.645**
Cough	8 (13.3)	18 (14.8)	0.495**
Pleuretic chest pain	15 (25)	30 (24.6)	0.545**
Hemoptysis	2 (3.3)	2 (1.6)	0.401**
Abnormal electrocardiography	7 (11.7)	11 (9)	0.374**
Tachycardia	22 (37.3)	48 (39.3)	0.495**
Hypotension	17 (28.3)	30 (30.3)	0.461**
Phase of pregnancy			
First trimester£	3 (5)	4 (3.4)	0.013**
Second trimester£	7 (11.7)	8 (6.9)	
Third trimester£	49 (81.7)	86 (74.1)	
Postpartum	1 (1.7)	18 (15.5)	
Abnormal D-dimer	52 (86.7)	104 (85.2)	0.462**
Ejection fraction	59.41±8.74	58.74±10.27	0.655*
Oxygen saturation	96.85±1.61	96.51±2.07	0.290*

Data are mean SD or, *n* (%). **χ²; *Independent sample *t*-test; £First trimester (weeks 1-13), second trimester (weeks 14-27), and third trimester (28 weeks and beyond).
CTPA=Computed tomography pulmonary artery; SD=Standard deviation

Table 2: The comparison of clinical and demographic characteristics of imaging results of the studied population

	Diagnostic (*n*=148), *n* (%)	Nondiagnostic (*n*=34), *n* (%)	*P*
Age (years)	30.08±6.18	30.70±6.33	0.597*
Twin pregnancy	5 (3.4)	1 (2.9)	0.688**
Hypertensive disorders			
Chronic hypertension	10 (6.8)	5 (14.8)	0.123*
Preeclampsia	6 (4.1)	1 (2.9)	0.612*
Clinical signs/symptoms			
Calf swelling	6 (4.1)	0	0.284*
Dyspnoea	143 (96.6)	33 (97.1)	0.688*
Cough	23 (15.5)	3 (8.8)	0.237*
Pleuretic chest pain	37 (25)	8 (23.5)	0.526*
Hemoptysis	4 (2.7)	0	0.434*
Abnormal electrocardiography	14 (9.5)	4 (11.8)	0.444*
Tachycardia	53 (36.1)	17 (50)	0.096*
Hypotension	44 (29.7)	10 (29.4)	0.575*
Phase of pregnancy			
First trimester£	4 (2.8)	3 (8.8)	0.044
Second trimester£	12 (8.5)	3 (8.8)	
Third trimester£	110 (77.5)	25 (73.5)	
Postpartum	16 (11.3)	3 (8.8)	
Abnormal D-dimer	128 (86.5)	28 (82.4)	0.350*
Ejection fraction	59.65±7.99	56.02±15.06	0.051**
Oxygen saturation	96.64±1.91	96±2.07	0.715**

Data are presented in mean±SD or *n* (%). £First trimester (weeks 1-13), second trimester (weeks 14-27), third trimester (28 weeks and beyond); *χ²; **Independent sample *t*-test.
SD=Standard deviation

Among all the pregnant women with nondiagnostic imaging, only three patients in the perfusion scan group were treated by a therapeutic dose of anticoagulant based on the physicians' decision.

Table 3: Rate of nondiagnostic study for pulmonary embolism by computed tomography and perfusion scan

	Perfusion scan	CTPA	*P*
Nondiagnostic (%)	25 (41.701)	9 (7.4)	<0.001
Unadjusted OR (95% CI)	8.96 (3.829-21.001)	1	<0.001
Adjusted OR (95% CI)*	15.911 (5.177-48.897)	1	<0.001

Data are % unless otherwise specified. *Adjusted was done for the gestational trimester at diagnosis, hypertension, ejection fraction, and tachycardia. CTPA=Computed tomography pulmonary angiography; CI=Confidence interval; OR=Odds ratio

In a further 3-month follow-up of the patients, none referred with any presentation of PE. Besides, there was no mortality due to PE among the studied population.

DISCUSSION

The diagnosis of PE in pregnant women remained a challenge worldwide, as it cannot be easily diagnosed through clinical presentations and physical examinations. In addition, the initiation of medical treatment blindly, only by consideration of the signs/symptoms, is not recommended because the anticoagulant regimens may be teratogenic. These factors indicate the need for other diagnostic imaging modalities; however, they may be harmful to the fetus because of irradiation.[13] Nevertheless, in order to early diagnose PE, imaging with the ultimate diagnostic ability is required. CTPA and perfusion scan are the most common modalities used for this aim.[6]

The current study's assessments revealed that CTPA was superior to perfusion scan, as nondiagnostic reports of CTPA accounted for 7.4% only as compared to 41.7% in perfusion scans. Besides, among those diagnosed as PE, 11 (9.01%) were diagnosed by CTPA and 3.3% by perfusion scan. Logistic regression assessments revealed that the nondiagnostic outcomes of perfusion scan are 8.96 folds more than CTPA, which increased to 15.911 folds by controlling the probable confounders. Another point of our study that reinforces the value of CTPA over perfusion scan was that none of the women undergoing CTPA with the nondiagnostic report were anticoagulant treated because of clinical presentation. In contrast, the physicians decided to treat three ones with nondiagnostic reports of perfusion scan just based on clinical presentations.

The previous studies in this regard have been conducted retrospectively with controversial results. This variability in results is probably due to the accuracy of methods and protocols used for the diagnosis of PE, availability of medical records, and comorbidities of the studied population.

In the study conducted by Scott *et al*., 386 scans were done among whom PE diagnosis was confirmed in 15 patients.

Only 3.2% of perfusion scans were nondiagnostic, whereas this rate increased to 8.3% in CTPA. The comparison of the two modalities revealed an insignificant difference. Therefore, they concluded that imaging is required to exclude PE diagnosis for pregnant females as clinical presentations cannot easily diagnose PE. Therefore, the risks and benefits of imaging modalities should be calculated to minimize morbidity and mortality. Nevertheless, in contrast to our study, the nondiagnostic outcomes of perfusion scan were remarkably less than CTPA.[14]

Another study presented PE in 3.7% of CTPA cases, whereas 5.6% of the images were nondiagnostic, among which half of them had normal perfusion scan. The latter group was primarily assessed by a perfusion scan, among which two (2.02%) ones had nondiagnostic reports, and both had normal CTPA. This study represented similar negative predictive value for both CTPA and perfusion scan, a finding that made the authors present other considerations such as radiation concern, radiographic results, alternative diagnosis, and equipment availability as the determinant of the choice modality for the exclusion of PE among pregnant females suspicion for PE.[15]

In a retrospective study on 46 pregnant patients undergone CTPA and 91 ones with V/Q scan, the two modalities had comparable results as PE was diagnosed in 16% versus 11%, was negative in 65% versus 70%, and was undetermined in 19% versus 19% of CTPA versus V/Q scan. Accordingly, they repeated the theory about the necessity of risk assessment to use each of these modalities in the pregnant females as a high-risk group rather than insisting on the diagnostic specificity of the imaging modalities.[16]

We assume that the utilized criteria for interpreting perfusion scan or the quality and modality of our device are responsible for these significant differences in our study by the other in the other communities.

The study of Ridge *et al*. compared 25 CTPA versus 25 perfusion scans on suspected females for PE and represented significantly more nondiagnostic reports in CTPA than the latter modality (35.7% vs. 4%). Comparing CTPA reports of pregnant versus nonpregnant cases was accompanied by a significantly worse condition among pregnant cases (35.7% vs. 2.1%), which shows the considerable impact of physiological changes during pregnancy on CTPA interpretation.[17] However in Moradi presented only 4.5% of nondiagnostic reports in their study of pregnant women who underwent CTPA.[18] Their outcomes were somewhat similar to our findings.

Another aspect that should not be underestimated is the characteristics of the device used for CTPA. For instance,

nondiagnostic or borderline reports in Anderson *et al.*' study were remarkably high as accounted for 62.5% of the images using a four-slice multidetector computed tomography.[19]

There is a concern about the fetus's exposure to the radiation, which is remarkably more in CTPA than the perfusion scan. This issue is an essential factor in selecting the type of diagnostic imaging. Fetus radiation exposure of up to 0.01 Gy in computed tomography may increase malignancy risk in the first and second decades of a lifetime.[20] Furthermore, the minimum dose for teratogenicity accounts for 0.1 Gy.[21] Nevertheless, radiation exposure by both CTPA (7 millisieverts [mSv]) and perfusion scan (2.5 mSv) are much lower than the mentioned above harmful values.[22,23] Another concern about the radiation of imaging modalities accounts for the increased risk of breast cancer for mothers, which can be appropriately prevented by the breast shields made of bismuth.[24,25]

In summary, CTPA had fewer nondiagnostic outcomes as compared to perfusion scan in this study. Nevertheless, due to the physiological changes in pregnancy, which may lead to nondiagnostic findings of CTPA, a practical guideline for the interpretation of CTPA in pregnancy is required. Another point to reinforce the diagnosis of PE or exclude this diagnosis is to apply different means concurrently. For instance, Well's criteria plus imaging or ultrasonographic studies plus imaging can lead to more definitive diagnoses.

Limitations
Small sample size and inability to assess all of the probable confounders affecting PE risks are the most remarkable limitations of the current study. Besides, as a ventilation scan was not available in our center, the perfusion scans were interpreted using the chest X-rays. Therefore, we recommend further studies using a ventilation-perfusion scan.

CONCLUSIONS

Current available clinical signs, symptoms, and laboratory tools are not adequate to exclude the pregnant patients suspected of PE. Regarding diagnostic challenging of PE, imaging has an essential role in excluding PE. Accordingly, the nondiagnostic rate of perfusion scan was 15-fold higher than CTPA in this study, making us prefer CTPA rather than perfusion scan. Nevertheless, further studies are strongly recommended to promote the generalizability of the outcomes.

Conflicts of interest
There are no conflicts of interest.

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