Shiraz E-Med J. 2021 February; 22(2):e100705. doi: 10.5812/semj.100705.

Published online 2020 June 13. **Research Article**

Evaluation of Pregnant Patients with Suspected Pulmonary Embolism: A Descriptive Cross-Sectional Study

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Received 2020 January 11; **Revised** 2020 March 29; **Accepted** 2020 March 29.

Abstract

Background: Pulmonary thromboembolism (PTE) is a leading cause of maternal mortality. However, diagnosis of PTE can be challenging during pregnancy, and there is no consensus regarding the best diagnostic approach.
Objectives: The current study aimed to evaluate the applicability of clinical symptoms and diagnostic tests in ruling in or ruling out PTE during pregnancy.
Methods: In this one-year, cross-sectional, descriptive study, we evaluated pregnant or postpartum (six weeks postpartum) women suspected of PTE, who were admitted to the internal medicine intensive care units (ICUs) of hospitals (Namazi and Shahid Faghihi hospitals), affiliated with Shiraz University, Shiraz, Iran, during August 2016-July 2017. The participants underwent electrocardiography (ECG), serum troponin-I and D-dimer measurements, chest X-ray, color-doppler sonography (CDS) of the lower extremity venous system, transthoracic echocardiography, pulmonary perfusion scan, or pulmonary computed tomography angiography (CTA). The participants' clinical manifestations were also assessed.
Results: A total of 103 women, with the mean age of 30.37 $\pm$ 5.35 years, were included in this study. Seventy-seven women underwent pulmonary CTA or pulmonary perfusion scan. PTE was documented in nine cases. Dyspnea was the most common symptom. The respiratory rate, cough, dizziness, and fever on admission had significant correlations with the final diagnosis of PTE (P = 0.01, 0.03, 0.007, and 0.04, respectively). The ECG study of one case with PTE showed right axis deviation, while the ECG findings of the other eight cases showed no specific pattern. The chest X-ray findings had no significant correlation with the final diagnosis of PTE. Overall, 38 women underwent CDS, one of whom presented with deep vein thrombosis. The serum D-dimer level was positive in three cases with documented PTE (normal in one patient with PTE), and the serum troponin-I level was positive in one case with the final diagnosis of PTE (normal level in two patients with PTE).
Conclusions: Based on the findings, clinical symptoms and biochemical tests alone are not reliable for ruling in or ruling out PTE during pregnancy, and CTA and pulmonary ventilation/perfusion scan should be performed for these cases.

Keywords: Chest Pain, Diagnosis, Dyspnea, Hemoptysis, Pregnancy, Pulmonary Embolism

1. Background

Venous thromboembolism (VTE) is one of the common and important etiologies of non-physiological dyspnea during pregnancy and postpartum period (particularly after cesarean section), which can cause considerable morbidity and mortality (1, 2). It is known that pregnancy increases the risk of thromboembolic events. Evidence shows that VTE has an incidence of 1 case per 1000 pregnancies and a mortality rate of 1.08 per 100,000 pregnancies in developed countries (3). Therefore, timely diagnosis and prompt management of thromboembolic events are of great importance and can be life-saving (4).

Nevertheless, diagnosis of pulmonary thromboembolism (PTE) during pregnancy can be challenging (5). On one hand, physiological changes of pregnancy can cause symptoms that mimic the clinical manifestations of PTE, and on the other hand, there are some limitations in the use of paraclinical and imaging studies during pregnancy (1, 6, 7). In addition, clinical prediction rules, which are used for pretest probability assessment of PTE, are not applicable during pregnancy (1). Use of imaging modali-

ties during pregnancy is also challenging, especially in the early phase, due to the possible adverse effects on the fetus and the mother (8, 9). Accordingly, practitioners sometimes rely on only clinical manifestations to manage pregnant women suspected of PTE, resulting in over-diagnosis or under-diagnosis of this condition.

2. Objectives

According to our literature review, there is no comprehensive data about PTE among pregnant or postpartum women suspected of this issue in our region. Therefore, in this study, we aimed to evaluate and document our findings about PTE and some of its aspects, which can influence our future approach.

3. Methods

This cross-sectional descriptive study was performed during one year from August 2016 until the end of July 2017. We documented the data of all pregnant and postpartum (six weeks postpartum) women with a possible diagnosis of PTE (women with a high-risk pregnancy), who were admitted to the internal medicine intensive care units (ICUs) of Namazi and Shahid Faghihi hospitals, as two referral and teaching centers affiliated with Shiraz University of Medical Sciences, Shiraz, Fars Province, Iran. All of the participants were evaluated using electrocardiography (ECG). Also, some of the subjects were assessed based on the first-line physician's judgment, using biochemical tests, including serum high-sensitivity troponin-I measurement by automated enzyme-linked fluorescence immunoassay (ELFA, VIDAS, bioMérieux®) and D-dimer measurement (Nycocard). It should be noted that the D-dimer tests in our study had different cut-off points (500 ng/mL and 0.3 mg).

In the next step, according to the pulmonologist's clinical decision, women suspected of PTE underwent plain chest radiography, color-doppler study (CDS) of the venous system in the lower extremities, transthoracic echocardiography (TTE), and finally, pulmonary perfusion scan or pulmonary computed tomography angiography (CTA) for definite diagnosis. Women who did not consent to undergo CTA or pulmonary perfusion scan and those with a serum creatinine level above 1.5 mg/dL were excluded. The Institutional Review Board and Ethics Committee of Shiraz University of Medical Sciences approved this study (thesis number: 15507; ethics committee code: 1397/160). All of the participants in the study signed a written informed consent.

Data were collected using a registration form. The subjects' demographic data (age and sex), medical and social history (e.g., use of waterpipe, cigarette, and alcohol), clinical manifestations, on-admission vital signs, laboratory data, and diagnostic test results were also collected. An experienced radiologist, unaware of the participants' final diagnosis, reported the findings of imaging studies, including CTA of pulmonary vessels and chest X-ray. The results of perfusion scans were also reported by a nuclear medicine specialist; it should be noted that we did not have the required facilities for pulmonary ventilation scan. We assessed the presence of the following symptoms in each participant: shortness of breath or rapid breathing, sharp chest pain, cough, hemoptysis, palpitation, dizziness, and fever.

Data analysis was performed using SPSS version 20 (SPSS Inc., Chicago, Ill., USA). Descriptive statistics, including mean, minimum, maximum, and standard deviation (SD), as well as prevalence rates, were measured for analyzing the collected data. Chi-square and independent sample *t*-test were also carried out. P value less than 0.05 was considered statistically significant.

4. Results

A total of 103 women with a high-risk pregnancy were included in the study, including 35 (33.98%) women, who were in the postpartum period (either after natural vaginal delivery or cesarean section). The mean age of the participants was 30.37 $\pm$ 5.35 years (minimum: 17 years; maximum: 43 years). The mean gestational age of pregnant women according to the last menstrual period was 194.16 $\pm$ 65.63 days (minimum: 30.00 days; maximum: 287.00 days). Three (2.91%) women had a history of cigarette smoking, and one (0.97%) woman had a history of waterpipe smoking.

Based on the findings, 77 (74.75%) out of 103 participants were finally evaluated using pulmonary CTA or pulmonary perfusion scan; four (3.88%) cases underwent both modalities. The rest of women (n = 26; 25.24%) did not undergo pulmonary CTA or pulmonary perfusion scan. In the latter group, PTE was ruled out based on the pulmonologist's clinical judgement, as their clinical manifestations were compatible with a diagnosis other than PTE. The follow-up of women for three months did not reveal VTE or organic cardiovascular disease.

Based on the ECG studies, as one of the first-line tools for the assessment of our cases, a total of 103 women were evaluated for findings suggestive of PTE. The ECG studies of 4 (3.88%) cases showed an inverted T-wave from V1 to V4 leads (none of them were diagnosed with PTE), 1 (0.97%) ECG showed right axis deviation (she was diagnosed with PTE), and ECGs of 7 (6.79%) women showed an S1Q3T3 pattern (none of them were diagnosed with PTE). No right

bundle branch block or QR pattern was seen in the V1 lead. The ECG study of 91 (88.34%) women showed a normal sinus rhythm. Also, 77 (74.75%) out of 103 women underwent chest X-ray. Cardiomegaly was the most common finding, while atelectasis was the least common. None of the chest X-ray findings had a significant correlation with the final diagnosis of PTE (Table 1).

Table 1. The Findings of Subjects' First Chest X-Ray and Its Correlation with the Final Diagnosis of Pulmonary Embolism (PTE)[a]

Radiographic Finding	Pulmonary Emboli	Number	P Value
Unilateral hemidiaphragm elevation	Yes	2 (2.59)	0.72
	No	19 (24.67)	
Consolidation	Yes	3 (3.89)	0.08
	No	14 (18.18)	
Pleural effusion	Yes	2 (2.59)	0.16
	No	9 (11.68)	
Focal oligemia	Yes	1 (1.29)	0.98
	No	12 (15.58)	
Atelectasis	Yes	1 (1.29)	0.09
	No	2 (2.59)	
Pulmonary artery enlargement	Yes	1 (1.29)	0.35
	No	25 (32.46)	
Cardiomegaly	Yes	2 (2.59)	0.57
	No	32 (41.55)	
Other finding	Yes	1 (1.29)	11.7
	No	8 (10.38)	

[a] Values are expressed as No. (%).

In the subgroup of 77 women, who were assessed using pulmonary CTA and/or pulmonary perfusion scan, shortness of breath was the most common clinical manifestation (n = 69; 89.6%), while hemoptysis was the least common (n = 4; 5.2%) (Table 2). In this subgroup of 77 women, among vital signs on admission, only respiratory rate had a significant correlation with the final diagnosis of PTE (P = 0.01); in other words, a higher respiratory rate increased the possibility of PTE. Positive history of cough, dizziness, and fever had significant correlations with the final diagnosis of PTE (P = 0.03, 0.007, and 0.04, respectively) (Table 2).

TTE was used as a diagnostic tool for 55 (71.4%) women, and 38 (49.4%) women underwent CDS of the lower extremity venous system. Moreover, CT angiography of pulmonary arteries was performed in 42 (54.5%) subjects, and 39 (50.6%) women were evaluated using pulmonary perfusion scan. Seven (16.66%) pulmonary CTAs were reported as positive for PTE (all cases were in the postpartum period), while 35 (83.33%) were normal. PTE was diagnosed using pulmonary perfusion scan in two pregnant women, while other pulmonary perfusion scans indicated the low probability of this condition. Four (5.19%) cases underwent both CT angiography of pulmonary arteries and pulmonary perfusion scan; however, none of them were diagnosed with PTE.

The TTE study of 6 (10.90%) women showed considerable abnormalities; two (3.63%) women showed evidence of peripartum cardiomyopathy. Valvular dysfunction was detected in 3 (5.45%) cases, and left ventricular systolic dysfunction was reported in 1 (1.81%) case. Two out of six women were diagnosed with PTE (one with submassive embolism), and their TTE results showed moderate to severe tricuspid valve regurgitation. The CDS of the lower extremity venous system was positive in 1 (1.2%) case for deep vein thrombosis.

Of 77 women, the serum D-dimer level was measured in 28 (36.3%) cases, 13 of whom (46.42%) had a positive serum D-dimer level; only three (23.07%) cases had documented PTE. In contrast, one case with documented PTE had a normal serum D-dimer level. Moreover, high-sensitivity serum troponin-I level was examined in 34 (44.1%) women. It was positive in only one patient with documented PTE (Table 3). We found no significant difference between women with and without a final diagnosis of PTE in terms of their on-admission O_2 saturation measured by pulse oximetry (P = 0.06) and blood gas parameters, including pH (P = 0.85) and partial pressure of carbon dioxide (PCO_2) (P = 0.29).

5. Discussion

In this descriptive cross-sectional study, we evaluated the data of women with high-risk pregnancies regarding PTE in two teaching referral hospitals of Shiraz, Iran. We found that the majority of women had no PTE. This finding is in agreement with previous studies, which documented the overdiagnosis of PTE in pregnant women (10). In our study, PTE was ruled out in some cases, based on the pulmonologist's clinical decision, who was in charge of the patients in the ICU without any imaging findings. This finding may highlight the fact that we have an inappropriate referral system for postpartum and pregnant women to evaluate suspected PTE. This may be due to the defensive practice and low skill of referring physicians or the external pressure by the Office for high-risk mothers (under the supervision of our university) on physicians for referring pregnant and postpartum women, even those with a low risk of a pathologic disease, to a larger referral center. We found a significant correlation between some of the

Table 2. Correlation of Clinical Manifestations with the Final Diagnosis of Pulmonary Embolism (PTE)[a]

Clinical Symptom	Symptom Positivity	Values	Final Diagnosis of PTE		P Value
			Yes	No	
Shortness of breath	Yes	69 (89.6)	8 (11.6)	61 (88.4)	0.94
	No	8 (10.4)	1 (12.5)	7 (87.5)	
Chest pain	Yes	38 (49.4)	7 (18.4)	31 (81.6)	0.07
	No	39 (50.6)	2 (5.1)	37 (94.9)	
Coughing	Yes	20 (26.0)	5 (25.0)	15 (75.0)	0.03
	No	57 (74.0)	4 (7.0)	53 (93.0)	
Hemoptysis	Yes	4 (5.2)	1 (25.0)	3 (75.0)	0.39
	No	73 (94.8)	8 (11.0)	65 (89.0)	
Palpitation	Yes	25 (32.5)	3 (12.0)	22 (88.0)	0.95
	No	52 (67.5)	6 (11.5)	46 (88.5)	
Dizziness	Yes	7 (9.1)	3 (42.9)	4 (57.1)	0.007
	No	70 (90.9)	6 (8.6)	64 (91.4)	
Fever	Yes	15 (19.5)	4 (26.7)	11 (73.3)	0.04
	No	62 (80.5)	5 (8.1)	57 (91.9)	

[a]Values are expressed as No. (%).

Table 3. The Findings of a Subgroup of Women (N = 77) in Terms of the Serum D-Dimer and Troponin-I Levels and Their Correlations with the Final Diagnosis of Pulmonary Embolism (PTE)[a]

	Positivity	Values	Final Diagnosis of PTE		P Value
			Yes	No	
D-dimer	Yes	13 (16.9)	3 (23.1)	10 (76.9)	0.34
	No	15 (19.5)	1 (6.7)	14 (93.3)	
Troponin-I	Yes	1 (1.3)	1 (100.0)	0 (0.0)	0.01
	No	33 (42.9)	2 (6.1)	31 (93.9)	

[a]Values are expressed as No. (%).

subjects' symptoms, including cough, dizziness, and fever, and the final diagnosis of PTE.

PTE is one of the major etiologies of maternal mortality in developed countries (5), possibly due to the increased risk of thromboembolic events during pregnancy, particularly in the postpartum period (11). It has been shown that the risk of VTE is four to five times higher in pregnant women (12). Another possible explanation for maternal death due to PTE can be the problematic diagnosis of this condition during pregnancy, leading to under- or over-diagnosis (5).

For different reasons, predictive clinical models, which help physicians in the evaluation of suspected PTE (like Wells' criteria and Genova score), have not been validated to be used during pregnancy (1). These models are generally designed based on the findings of studies on non-pregnant populations. Moreover, some of the items in these scoring systems, such as diagnosis of an active malignancy or age above 65 years, may be completely irrelevant in pregnant women. On the other hand, some criteria, such as dyspnea, tachycardia, and edema of lower extremities, may be seen physiologically in normal pregnancy (1). In addition, assessment of an alternative diagnosis of PTE can be more problematic among pregnant women (1).

Although previous studies have suggested a combination of modified Well's score and trimester-specific D-dimer level for categorizing pregnant women into high-risk and low-risk groups of PTE, there is yet no consensus for using this approach in clinical practice. Also, some previous studies have discouraged the use of D-dimer measurement for evaluating suspected emboli during pregnancy (2, 5, 13). In this regard, a study by Goodacre et al. (14) showed that the patients' clinical manifestations, clinical decision rules, and D-dimer test are not reliable tools

for assessing pregnant or postpartum women with suspected PTE. In fact, the specificity of D-dimer test decreases considerably during pregnancy, particularly in the third trimester (about 0%), considering the diagnostic serum levels used for non-pregnant cases (12). Therefore, we did not calculate the subjects' Wells' score in our research.

On the other hand, regarding the D-dimer and serum troponin-I levels, our findings showed that this laboratory test could not be completely reliable for ruling in or ruling out PTE during pregnancy. We found that although a negative D-dimer result reduces the risk of PTE, it cannot definitely rule out this condition, as one of our patients with a final diagnosis of PTE had a normal serum D-dimer level. This finding is also true for serum troponin-I level, as our results showed that two cases with normal serum troponin-I levels had PTE.

Both pulmonary CTA and pulmonary ventilation-perfusion scan can safely rule out PTE during pregnancy (8). Although pulmonary ventilation-perfusion scanning exposes the mother to lower doses of radiation compared to CT scan, the probability of non-diagnostic findings is higher than pulmonary CTA, which necessitates further imaging studies (8, 9). There are also some concerns regarding the use of pulmonary CT angiography during pregnancy, including radiation exposure of the mother and fetus, risk of contrast-induced nephropathy, risk of neonatal thyroid function depression after exposure to the iodine contrast, and possibility of allergic reaction to the contrast agent (9). The main concern about radiation exposure is its possible carcinogenic effects on the mother's breast tissue (9). It should be noted that factors, such as the CT scanner model, imaging protocol, and pregnancy trimester, can affect radiation exposure (9).

Our findings showed that there is no significant correlation between the findings of plain chest radiography and PTE during pregnancy. However, a previous study by Goodacre et al. (14) found that the presence of chest X-ray abnormalities, irrespective of the type of abnormality, could increase the likelihood of PTE; this may be due to the further assessment of these cases for determining the cause of radiographic abnormality. Moreover, our findings showed that ECG findings, which suggest PTE in non-pregnant populations, cannot be reliable for the diagnosis of PTE during pregnancy. It is worth mentioning that none of our subjects with an S1Q3T3 pattern had PTE. This ECG finding suggests acute cor-pulmonale and may be associated with conditions, such as pneumothorax, more severe forms of PTE, and severe bronchospasm in non-pregnant cases (15). Overall, it is necessary to evaluate the prevalence and significance of this ECG abnormality in an adequately powered study on pregnant women.

In the present study, PTE diagnosis was confirmed in only 9 (8.73%) women, who were hospitalized for the evaluation of suspected PTE. One possible explanation for this finding can be that junior residents with less knowledge and clinical experience visit all of these women in our centers as the first-line approach and make their first judgments. It seems that this approach needs to be modified for different reasons. It should be noted that we practice medicine in limited-resource centers with a limited number of hospital and ICU beds and a limited number of healthcare and nursing personnel. In addition, the current approach may expose women to different risks as discussed above. Therefore, not all pregnant and postpartum women suspected of PTE need to be hospitalized in ICUs, as they can be managed in general internal medicine or pulmonary wards (16). Admission of these women in ICU wards can create some problems, such as exposure to multidrug-resistant microorganisms in ICUs and deprivation of other patients from ICU beds. To achieve this goal, we recommend the development of local diagnostic and management protocols or adherence to a well-established algorithm to avoid wasting resources and prevent harm to patients.

To the best of our knowledge, pregnancy-adapted YEARS algorithm is the most recent well-known protocol for evaluating pregnant women with suspected PTE (17, 18). It has been shown that the use of this algorithm reduces the emergency department visit time and has economic benefits (19). The YEARS algorithm first examines the presence or absence of clinical findings, such as deep vein thrombosis of the lower extremities, hemoptysis, and clinical risk of PTE. In the next step, the findings of compression ultrasonography of the lower limb veins and serum D-dimer level are evaluated.

Several studies have examined the clinical application of YEARS algorithm and reported its efficacy in ruling out acute PTE among pregnant women, which is associated with a considerable reduction in the number of pulmonary CT angiograms (17, 18). However, some factors may negatively influence the applicability of this algorithm. For instance, pelvic veins are the most common site of deep vein thrombosis during pregnancy, and doppler ultrasound of the lower extremity venous system may not detect them and may produce false negative results (6). Moreover, a study by Kabrhel et al. (20) showed that use of different D-dimer cut-off points in different centers can increase the number of missed pulmonary embolisms. On the other hand, some other studies advocate the use of different cut-off points based on pretest clinical probability (21).

Among pregnant and postpartum women included in our research, none of them had clinical signs of lower extremity deep vein thrombosis. However, according to the

traditional approach, about half of our subjects underwent CDS of the lower extremity venous system; these studies yielded positive results in only one case. In spite of the YEARS algorithm limitations, we suggest its application in our region because of its obvious benefits; however, application of this approach in clinical practice has some prerequisites. For instance, the serum D-dimer level should be measured using a unique and standard method.

One limitation of current study was the limited study population; therefore, further large-scale studies are required to evaluate the burden of thromboembolic events among pregnant and postpartum women in our region and to recognize the pitfalls of management. The second limitation of this study was the lack of access to pulmonary ventilation scan facilities.

In conclusion, we found that use of clinical symptoms and biochemical tests, including serum D-dimer and troponin-I levels, alone is not reliable for ruling in or ruling out PTE among pregnant or postpartum women. TTE can be helpful for ruling out other possible diagnoses, but it cannot predict the presence or absence of acute PTE during pregnancy, particularly its subsegmental form. It seems that pulmonary CTA and pulmonary ventilation-perfusion scan, together with a careful history-taking and physical examination, are the best practical tools for ruling in or ruling out the diagnosis of PTE; however, their benefits should be weighed against their possible harms.

Footnotes

Authors' Contribution: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Mohammad Javad Fallahi, Behnam Dalfardi, Reza Jalili, Seyed Masoom Masoompour, Behrouz Momeni, and Seiyed Mohammad Ali Ghayumi. The first draft of the manuscript was written by Behnam Dalfardi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: The Institutional Review Board and Ethics Committee of Shiraz University of Medical Sciences approved this study (Ethics Committee code: 1397/160).

Funding/Support: This study was supported by Shiraz University of Medical Sciences.

Informed Consent: All of the women included in this study signed a written informed consent form.

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