

## An Official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline: Evaluation of Suspected Pulmonary Embolism In Pregnancy

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**Background:** Pulmonary embolism (PE) is a leading cause of maternal mortality in the developed world. Along with appropriate prophylaxis and therapy, prevention of death from PE in pregnancy requires a high index of clinical suspicion followed by a timely and accurate diagnostic approach.

**Methods:** To provide guidance on this important health issue, a multidisciplinary panel of major medical stakeholders was convened to develop evidence-based guidelines for evaluation of suspected pulmonary embolism in pregnancy using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. In formulation of the recommended diagnostic algorithm, the important outcomes were defined to be diagnostic accuracy and diagnostic yield; the panel placed a high value on minimizing cumulative radiation dose when determining the recommended sequence of tests.

**Results:** Overall, the quality of the underlying evidence for all recommendations was rated as very low or low, with some of the evidence considered for recommendations extrapolated from studies of the general population. Despite the low-quality evidence, strong recommendations were made for three specific scenarios: performance of chest radiography (CXR) as the first radiation-associated procedure; use of lung scintigraphy as the preferred test in the setting of

a normal CXR; and performance of computed-tomographic pulmonary angiography (CTPA) rather than digital subtraction angiography (DSA) in a pregnant woman with a nondiagnostic ventilation-perfusion (V/Q) result.

**Discussion:** The recommendations presented in this guideline are based upon the currently available evidence; availability of new clinical research data and development and dissemination of new technologies will necessitate a revision and update.

### EXECUTIVE SUMMARY

The diagnostic algorithm for evaluation of suspected pulmonary embolism (PE) in pregnancy presented in this clinical practice guideline represents the collective efforts of a multidisciplinary panel of major medical stakeholders who developed these recommendations using the GRADE system (Figure 1). A major strength of these guidelines is the transparent evidence-based approach with explicit description of the values that influenced the recommendations; the main weaknesses are the low quality and very limited amount of direct evidence pertaining to diagnostic test accuracy and patient-important outcomes in the pregnant population. The diagnostic algorithm was formulated under the assumptions that patients are stable and all studies are equally available. In real-life situations where either the patient is unstable or some studies are not available on a timely basis, empiric initiation of therapy and/or alternate diagnostic strategies should be considered.

**Recommendation 1.** In pregnant women with suspected PE, we suggest that D-dimer not be used to exclude PE (weak recommendation, very-low-quality evidence).

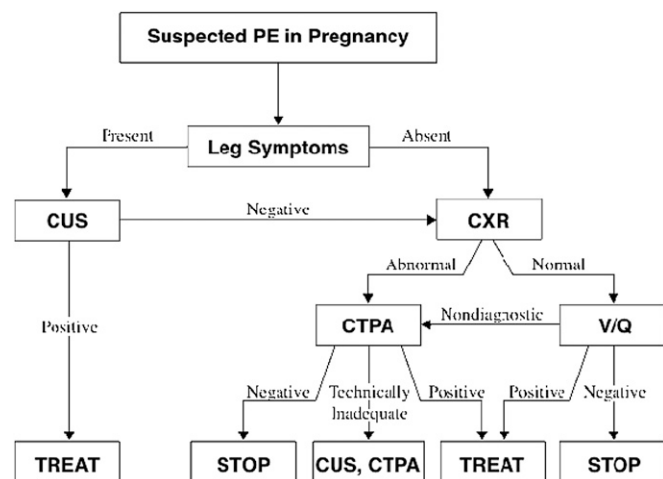
**Recommendation 2.** In pregnant women with suspected PE and signs and symptoms of deep venous thrombosis (DVT), we suggest performing bilateral venous compression ultrasound (CUS) of lower extremities, followed by anticoagulation treatment if positive and by further testing if negative (weak recommendation, very-low-quality evidence).

**Recommendation 3.** In pregnant women with suspected PE and no signs and symptoms of DVT, we suggest performing studies of the pulmonary vasculature rather than CUS of the lower extremities (weak recommendation, very-low-quality evidence).

**Recommendation 4.** In pregnant women with suspected PE, we recommend a CXR as the first radiation-associated procedure

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**Figure 1.** Diagnostic algorithm for suspected PE in pregnancy.

in the imaging work-up (strong recommendation, low-quality evidence).

**Recommendation 5.** In pregnant women with suspected PE and a normal CXR, we recommend lung scintigraphy as the next imaging test rather than CTPA (strong recommendation, low-quality evidence).

**Recommendation 6.** In pregnant women with suspected PE and a nondiagnostic  $\dot{V}/\dot{Q}$  scan, we suggest further diagnostic testing rather than clinical management alone (weak recommendation, low-quality evidence). In patients with a nondiagnostic  $\dot{V}/\dot{Q}$  scan in whom a decision is made to further investigate, we recommend CTPA rather than DSA (strong recommendation, very-low-quality evidence).

**Recommendation 7.** In pregnant women with suspected PE and an abnormal CXR, we suggest CTPA as the next imaging test rather than lung scintigraphy (weak recommendation, very-low-quality evidence).

## INTRODUCTION

Pulmonary embolism (PE) is a leading cause of pregnancy-related mortality in the developed world, accounting for 20% of maternal deaths in the United States (1). Accurate clinical diagnosis of venous thromboembolism (VTE) in pregnancy is notoriously difficult due to the overlap of signs and symptoms between physiologic changes of pregnancy and development of PE or deep venous thrombosis (DVT) (2); VTE is ultimately confirmed in less than 10% of pregnant women who present with concerning clinical features (2). Although an array of diagnostic tests is currently available, clinicians confronted with management of a pregnant woman with suspected PE are often uncertain as to the best diagnostic algorithm to follow. Opinion papers and practice surveys exist, but are inconsistent in their approaches (2–6). To provide guidance on this important health issue, a multidisciplinary panel including major medical stakeholder groups was convened to develop evidence-based guidelines using currently available data.

## METHODS

### Practice Guideline Panel

These guidelines were developed conforming to American Thoracic Society guidelines (Table 1) and using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (7). The Pulmonary Circulation Assembly of the American Thoracic Society and the Society of Thoracic

Radiology co-sponsored the project. Invitations for society participation extended to the sitting presidents of the American College of Obstetricians and Gynecologists and Society of Nuclear Medicine resulted in assignment of members of these societies to the working panel. The group developing the guidelines included cardiothoracic radiologists and nuclear medicine physicians with expertise in imaging of pulmonary embolism, pulmonologists and obstetrician/gynecologists with expertise in diagnosis and management of pregnant women with suspected PE, medical physicists, medical ethicists with expertise in maternal-fetal health issues, and a methodologist as shown in Table 2.

### Formulation of Questions and Definition of Important Outcomes

Panel co-chairs working with the methodologist initially identified the questions, which subsequently were refined by the entire working group. The clinical questions covered by the guidelines are listed in Table 3. Questions were categorized as being either descriptive or actionable in nature, with the intent to develop recommendations only for actionable questions. The majority of descriptive questions were included to provide evidence for development of the recommendations for the diagnostic algorithm. The important outcomes for questions related to diagnostic tests were defined to be diagnostic accuracy and diagnostic yield. For each test, diagnostic yield was defined as the percentage of studies that were of an acceptable technical quality and provided the necessary information to establish a diagnosis.

### Literature Search and Preparation of Evidence Tables

To identify the relevant evidence, two research librarians working in conjunction with the panel co-chairs developed an extensive series of search strategies addressing each of the clinical questions (see Appendix E1 in the online supplement). Searches were run in PubMed (January 1990 to July 2010) and the Cochrane Library. The search strategies excluded non-English language articles and, in some cases, editorials and letters to the editor. All PubMed searches were saved in a shared “My NCBI” account for review and editing by panel members.

**TABLE 1. METHODS SUMMARY**

| Methods Checklist                                                                                                                                                                                          | Yes | No |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|
| Panel assembly:                                                                                                                                                                                            |     |    |
| ● Included experts from relevant clinical and non-clinical disciplines                                                                                                                                     | x   |    |
| ● Included individual who represents views of patients and society at large                                                                                                                                | x   |    |
| ● Included methodologist with appropriate expertise (documented expertise in development of conducting systematic reviews to identify the evidence base and development of evidence-based recommendations) | x   |    |
| Literature review:                                                                                                                                                                                         |     |    |
| ● Performed in collaboration with librarian                                                                                                                                                                | x   |    |
| ● Searched multiple electronic databases                                                                                                                                                                   | x   |    |
| ● Reviewed reference lists of retrieved articles                                                                                                                                                           | x   |    |
| Evidence synthesis:                                                                                                                                                                                        |     |    |
| ● Applied pre-specified inclusion and exclusion criteria                                                                                                                                                   | x   |    |
| ● Evaluated included studies for sources of bias                                                                                                                                                           | x   |    |
| ● Explicitly summarized benefits and harms                                                                                                                                                                 | x   |    |
| ● Used PRISMA to report systematic review                                                                                                                                                                  |     | x  |
| ● Used GRADE to describe quality of evidence                                                                                                                                                               | x   |    |
| Generation of recommendations:                                                                                                                                                                             |     |    |
| ● Used GRADE to rate the strength of recommendations                                                                                                                                                       | x   |    |

*Definition of abbreviations:* GRADE = Grades of Recommendation, Assessment, Development, and Evaluation; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

**TABLE 2. GUIDELINE PANEL COMPOSITION**

|                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Panel (Voting)                                                                                                                                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>● Four cardiothoracic radiologists and two nuclear medicine physicians with expertise in imaging of pulmonary embolism</li> <li>● Three obstetrician/gynecologists and two pulmonologists with expertise in diagnosis and management of suspected pulmonary embolism in pregnant women</li> </ul> |
| Review Team                                                                                                                                                                                                                                                                                                                              |
| <ul style="list-style-type: none"> <li>● Eight reviewers, including one methodologist with experience using the Grading Recommendations, Assessment, Development, and Evaluation (GRADE) approach</li> </ul>                                                                                                                             |
| Other Stakeholders                                                                                                                                                                                                                                                                                                                       |
| <ul style="list-style-type: none"> <li>● Two ethicists with expertise in fetal-maternal health issues</li> <li>● Two medical physicists</li> </ul>                                                                                                                                                                                       |

Under the direction and supervision of a co-chair and the methodologist, a group of eight independent panel members reviewed the results of the literature search and compiled the data into structured evidence tables. For questions with sparse or nonexistent data specific to the pregnant population, data from the general population were included. Using the GRADE approach, evidence was classified as high, moderate, low or very low quality; assessments of the quality of evidence took into account the study design, limitations of the study, directness of evidence, and consistency of evidence across studies. Given frequently encountered study limitations such as nonconsecutive patient enrollment, retrospective design, indirect population, low precision, and indirect outcomes rather than patient-important outcomes such as morbidity or mortality, the overall quality of evidence was judged to be low or very low for each of the clinical questions. Evidence tables with accompanying summary text were posted on an online repository (RefWorks) for review by committee members prior to discussion and voting.

### Panel Meeting and Conference Call

One face-to-face meeting of the panel was held to discuss the results of the evidence review and the procedure to develop recommendations. The committee agreed that recommendations would be based on a consensus of the group and that voting

**TABLE 3. CLINICAL QUESTIONS**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>● What are the clinical indications for imaging evaluation of suspected pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● Should D-dimer be used to exclude suspected pulmonary embolism in a pregnant woman? (Actionable)</li> <li>● What are the risks to mother and fetus when studies requiring radiation are performed? (Descriptive)</li> <li>● What are the risks to the fetus when studies requiring contrast (iodinated intravenous and gadolinium-based media) are performed on a pregnant woman? (Descriptive)</li> <li>● What is the value of a chest radiograph in the diagnostic assessment of suspected pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● What is the value of bilateral venous compression ultrasound of lower extremities in the diagnostic assessment of suspected pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● What is the value of lung scintigraphy in the diagnostic assessment of suspected pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● What is the value of a computed tomographic pulmonary angiogram in the diagnostic assessment of pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● What is the value of a magnetic resonance pulmonary angiogram in the diagnostic assessment of suspected pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● What is the value of digital subtraction angiography in the diagnostic assessment of suspected pulmonary embolism in a pregnant woman? (Descriptive)</li> <li>● What is the optimal imaging paradigm for suspected pulmonary embolism in a pregnant woman? (Actionable)</li> </ul> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

would be used if agreement could not be reached. In areas of continuing disagreement, a recommendation for or against a particular test (compared with a specific alternative) required at least 50% of participants in favor, with less than 20% preferring the alternative. Failure to meet this criterion would result in no recommendation; for a recommendation to be graded as strong rather than weak, at least 70% of participants were required to endorse it as strong. Adhering to these guidelines, recommendations were developed during two subsequent conference calls.

### Balance of Benefits, Harms, Burden, and Cost and Developing Recommendations

Recommendations were classified as “strong” or “weak” as recommended by the GRADE working group. Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs, and values. A high value was placed on minimizing radiation dose to mother and fetus when determining the recommended sequence of tests in the diagnostic algorithm. Agreement on the type and wording of the recommendations was reached during the conference call by consensus. However, three recommendations (#1: use of D-dimer; #6: nondiagnostic V/Q; and #7: abnormal CXR) required voting to decide the strength of the recommendation or whether the recommendation should be given at all. Taking into account the overall low quality of evidence, we have supplemented most recommendations with a statement on values and preferences that influenced our recommendations. We acknowledge the subjective nature of these values and expect that individuals with a different set of values may reach different conclusions.

### RESULTS

Evidence tables (Appendix E2) were prepared for seven of the clinical questions shown in Table 3. At present, there have been no randomized trials or even prospective studies with a reference standard to evaluate any diagnostic test's performance and accuracy in detection of PE in the pregnant population. In the absence of high-quality data on diagnostic accuracy of lung scintigraphy and computed tomographic pulmonary angiography (CTPA) in the pregnant population, the panel agreed to use diagnostic yield as an outcome surrogate. In all studies, we explicitly searched for management data (i.e., indication of clinical course of patient managed according to a particular strategy). Given the sparseness of data, some of the evidence considered for recommendations derived from studies of the general population; care was taken to clearly indicate when data from the nonpregnant population was considered in the formulation of recommendations.

### Diagnostic Algorithm

In considering the diagnostic algorithm, the important outcomes were defined as diagnostic accuracy and diagnostic yield. In making recommendations and considering their strength, the panel placed a higher value on minimizing radiation dose and a lower value on test rapidity, test potential to provide alternate diagnosis, and cost. The panel also considered the potential for a mortal outcome in scenarios in which diagnostic tests are interpreted as “nondiagnostic,” and correspondingly placed a higher value on diagnostic certainty and a lower value on minimizing radiation dose and cost.

*What are the clinical indications for imaging evaluation of suspected PE in a pregnant woman? (Descriptive).* The clinical indications reported in the literature for imaging evaluation of suspected PE in pregnancy include shortness of breath, pleuritic chest pain, hypoxemia, tachycardia, and to a lesser extent tachypnea,

hemoptysis, syncope, cough, unexplained hypotension, and other types of chest pain (8, 9). In a study of 38 pregnant women with confirmed PE, dyspnea (62%), pleuritic chest pain (55%), cough (24%), and sweating (18%) were the four most common features at presentation (10); Powrie and coworkers (11) reported an abnormal alveolar–arterial gradient ( $\geq 15$  mm Hg) in 8 of 17 (58%) pregnant women with confirmed PE.

Cahill and colleagues (9) evaluated the predictive value of six presenting clinical features (chest pain, dyspnea, desaturation, tachycardia, increased A–A gradient, and  $\text{PaO}_2 < 65$  mm Hg) in 304 pregnant and postpartum women with clinical suspicion for PE, and found no significant risk association between any individual or group of features and the presence of PE. Although some specific risk factors have been identified, at present there are no validated clinical prediction guidelines such as the Wells or Geneva criteria for determining pre-test probability of PE in the pregnant population (6, 12). The decision as to who to refer for imaging evaluation is complicated by the fact that some signs and symptoms such as mild subjective shortness of breath, tachycardia, and leg edema may accompany normal pregnancy. Clinicians must generally rely on their clinical judgment and employ a high index of suspicion.

**Should D-dimer be used to exclude suspected PE in a pregnant woman? (Actionable, Evidence Table E1).** Direct data comes from a retrospective study of 37 pregnant women with suspected PE who had both  $\dot{V}/\dot{Q}$  scans and D-dimer testing using the MDA Auto-dimer (immunoturbidimetric) assay (13). Sensitivity and specificity of D-dimer for suspected PE was calculated to be 73% and 15%, respectively, and the negative-likelihood ratio was 1.8, suggesting that a negative D-dimer is inadequate to rule out PE in pregnancy. In addition, two case reports have documented negative D-dimer levels in the setting of acute PE in pregnancy (14, 15).

Indirect evidence derives from three prospective studies ( $n = 389$ ) that evaluated accuracy of D-dimer testing for the diagnosis of DVT in pregnancy. Each study showed D-dimer to be 100% sensitive for DVT, but the number of positive DVT studies was low and specificities ranged from 6 to 23% using standard cut-points for the different assays (16–18). There has been one case report of a negative D-dimer test in the setting of acute calf DVT in pregnancy (19).

Based upon this sparse and indirect evidence, which included reports of false negative D-dimers in pregnant women with documented PE, panel members judged that D-dimer cannot currently be used to exclude suspected PE in pregnancy. Consideration of the additional cost and delay to diagnosis imposed by this test resulted in a weak recommendation not to include it in the diagnostic algorithm.

**What are the risks to mother and fetus when diagnostic studies requiring radiation are performed? (Descriptive).** Fetal radiation doses delivered *in utero* by properly performed diagnostic tests such as those used for suspected PE in the mother present no measurably increased risk of prenatal death, malformation, or impairment of mental development over the background incidence of these entities (20). Further, guidance issued from the National Council of Radiation Protection and Measurements states that “the risk [of abnormality] is considered to be negligible at 50 mGy or less when compared with other risks of pregnancy” (21).

Carcinogenesis induced by low-level radiation is considered the major risk for both fetus and mother. Although direct data are sparse, the currently accepted linear no-threshold model hypothesizes that ionizing radiation can cause cancer at any dose; risk of cancer is thought to be dependent upon age at exposure and to be linearly related to cumulative organ dose with risk additive for multiple studies or multiple episodes of diagnostic test malignancy to develop in childhood after *in utero* exposure (22).

In the exposed woman, lung and breast cancer are the two malignancies that account for the greatest risk of radiation-induced cancer mortality (23). Table 4 shows measured radiation doses to fetus and mother associated with diagnostic tests for suspected PE in pregnancy. The wide range of values for some tests reflects heterogeneity in the protocols and equipment used as well as differences in size and age of fetus at time of exposure.

**What are the risks to the fetus when studies requiring contrast (iodinated intravenous and gadolinium-based media) are performed on a pregnant woman? (Descriptive).** Direct evidence evaluating the risk of intravenous contrast to the fetus is sparse. Both iodinated and gadolinium contrast agents cross the placenta and enter both the fetal circulation and the amniotic fluid after intravenous administration. The main risk of iodinated contrast agents is related to the presence of free iodine with possible induction of neonatal hypothyroidism. A retrospective study of 344 pregnant women who underwent a CTPA exam for suspected PE found normal thyroxine levels in all neonates at time of birth (24). No animal studies have demonstrated teratogenicity to the developing fetus from iodinated contrast. Iodinated contrast agents are classified as category B by the U.S. Food and Drug Administration (FDA) (25).

The main risk to the fetus from gadolinium administration is exposure to potentially free unchelated gadolinium in the amniotic fluid. Animal studies have demonstrated teratogenic effects, but only at markedly increased doses and/or for extensive periods of exposure (26). Limited human observational studies have not documented any adverse fetal effects (27). Gadolinium-based contrast agents are classified as category C by the FDA (25).

**What is the value of a chest radiograph (CXR) in the diagnostic assessment of suspected PE in a pregnant woman? (Descriptive, Evidence Table E2).** Indirect evidence derived from studies in the general population show no radiographic findings sensitive or specific for PE (28, 29). Worsley and colleagues (28) reviewed radiographs of 1,063 nonpregnant patients enrolled in the PIOPED I trial and found no significant difference in the prevalence of areas of increased parenchymal opacity or vascular redistribution (early edema pattern) in the right hemithorax between patients with and without proven PE. Rarely, CXR may allow a confident, alternate diagnosis such as pneumothorax that can result in avoidance of further testing for PE.

Ideally, a CXR is obtained in every patient who undergoes a  $\dot{V}/\dot{Q}$  study because correlation with radiographic findings is integral to the interpretation of abnormal  $\dot{V}/\dot{Q}$  results (30). Use of chest radiographs to selectively triage only patients with normal CXR findings to undergo  $\dot{V}/\dot{Q}$  scan can increase the prevalence of definitive  $\dot{V}/\dot{Q}$  results (31, 32). Two studies ( $n = 105$  and 24) performed in pregnant women with suspected PE have reported definitive  $\dot{V}/\dot{Q}$  results (normal and high probability) in 94% and 96% of cases when the presenting CXR is normal (33, 34); in the larger of the two series, patients with asthma and chronic obstructive pulmonary disease (COPD) were also excluded from undergoing  $\dot{V}/\dot{Q}$  scans. In a study of 304 pregnant and postpartum women, patients with normal CXRs were

**TABLE 4. FETAL AND MATERNAL RADIATION DOSES ASSOCIATED WITH DIAGNOSTIC TESTS FOR PULMONARY EMBOLISM**

| Diagnostic Test   | Fetal Dose (mGy) | Maternal Dose (Whole Body Effective Dose in mSv) |
|-------------------|------------------|--------------------------------------------------|
|                   |                  |                                                  |
| CXR               | 0.002            | 0.1                                              |
| $\dot{V}/\dot{Q}$ | 0.32 – 0.74      | 1–2.5                                            |
| CTPA              | 0.03 – 0.66      | 4–18                                             |
| DSA               | —                | 7–28                                             |

significantly more likely to obtain a diagnostic result with  $\dot{V}/\dot{Q}$  scan than CTPA (94% versus 70%,  $P < 0.01$ ), whereas patients with abnormal CXRs had a significantly higher nondiagnostic study rate on  $\dot{V}/\dot{Q}$  scan than CTPA (40% v 16.4%,  $P < 0.01$ ) (9).

**What is the value of bilateral venous compression ultrasound (CUS) of lower extremities in the diagnostic assessment of suspected PE in a pregnant woman? (Descriptive, Evidence Table E3).** Direct evidence for the use of bilateral CUS of the lower extremities for diagnosis of PE in pregnancy currently does not exist. The benefit in use of ultrasound early in the diagnostic algorithm is potential avoidance of radiation-associated tests in the setting of a positive study.

The prevalence of DVT in pregnant women who present with suspected PE is unknown; however, the prevalence of ultimately diagnosed PE in this population is low and ranges from 3 to 6% (8, 9, 33). In the general population with suspected PE, the prevalence of DVT has been reported to be 9 to 12% when the prevalence of PE is 20 to 36% (35, 36). Using a DVT prevalence of 9%, Righini and colleagues (35) calculated the number needed to test—that is, the number of patients in whom an ultrasound should be undertaken to diagnose one clot and avoid further work-up—is around 11. In the pregnant population, the panel estimated that the number to test would likely be several-fold higher due to the lower prevalence of PE. In a series by Chan and coworkers (8), 67 of 121 (55%) consecutive pregnant women who presented with suspected PE underwent either bilateral CUS or impedance plethysmography; all results were negative.

Selection of women with signs and symptoms of DVT could increase the positive yield of CUS, as observed in the general population who present with suspected PE (35). In two clinical studies ( $n = 249$  and  $149$ ) (16, 18), the prevalence of DVT in pregnant women presenting with signs and symptoms of DVT were 7% and 9%. Chan and colleagues (37) have reported three objective variables (“LEfT”: symptoms in the left leg [L]; calf circumference difference  $\geq 2$  cm [E]; and first trimester presentation [Ft]) to be highly predictive of DVT in pregnancy; in their study of 194 pregnant women, the presence of two or three of these variables was associated with DVT in 58.3% (confidence interval, 35.8–75.5%) of cases.

**What is the value of lung scintigraphy in the diagnostic assessment of suspected PE in a pregnant woman? (Descriptive, Evidence Table E4).** Lung scintigraphy is a diagnostic imaging test that uses a radiopharmaceutical agent to assess pulmonary perfusion, and often includes a ventilation scan (38). Direct evidence for the use of lung scintigraphy derives from four retrospective management studies performed in the pregnant population that reported the prevalence of diagnostic  $\dot{V}/\dot{Q}$  scan results (high probability, very low probability, and normal) to range from 75 to 94%, with the upper value observed in a group selected by normal CXR and no prior history of asthma or COPD (8, 33, 39, 40). Lung scintigraphy consisted of combined ventilation and perfusion scans in two studies (8, 40) and perfusion (Q) scan alone in the other two studies (33, 39). In the studies by Scarsbrooke and coworkers (33) and Shahir and colleagues (39) that performed perfusion scans only, all completed Q scans with results other than high probability had a 100% negative predictive value for PE; in the remaining two studies where anticoagulation was administered to some patients with normal and nondiagnostic results, no subsequent VTE was observed in the untreated patients (8).

**What is the value of a CT pulmonary angiogram in the diagnostic assessment of PE in a pregnant woman? (Descriptive, Evidence Table E5).** A recent retrospective management study comparing CTPA ( $n = 106$ ) to Q scan ( $n = 99$ ) in the diagnosis of PE

in pregnancy has reported negative predictive values of 99% and 100%, respectively (39). In contrast to four other studies ( $n = 216$ ) (9, 34, 40, 41) performed in pregnant and postpartum women that reported technically inadequate CTPA exams in 17 to 36% of cases, this series by Shahir and coworkers (39) observed only 6% of CT exams to be inadequate for diagnosis. A study evaluating a low-dose CTPA protocol similarly showed no difference in image quality between pregnant women and nonpregnant control subjects, who received a standard dose technique (42). Clinically significant findings are found in 12 to 13% of pregnant patients who undergo CTPA, with the two most common being pneumonia (5–7%) and pulmonary edema (2–6%) (39, 40). In the study by Shahir and colleagues (39), 9 of 14 (64%) significant findings identified on CTPA were also visible on the presenting CXR.

**What is the value of a magnetic resonance pulmonary angiogram (MRPA) in the diagnostic assessment of suspected PE in a pregnant woman? (Descriptive, Evidence Table E6).** No accuracy or management studies that evaluate the performance of MRPA for PE in pregnancy have been performed. In the general population, data on performance of noncontrast-enhanced MRPA sequences for detection of PE is sparse. Using a real-time, steady-state free precession technique in 62 nonpregnant patients with suspected PE, Kluge and coworkers (43) reported a sensitivity of 85% and a specificity of 98%.

In the pregnant population, contrast-enhanced MRPA is relatively contraindicated due to the uncertain long-term effects of gadolinium on the fetus (44). In the general population, gadolinium-enhanced MRPA has been reported to have sensitivities ranging from 31 to 92% and specificities ranging from 85 to 100% (43, 45–49). In a recent large multicenter prospective study (50), gadolinium-enhanced MRPA was found to be technically inadequate in 25% of patients; in patients with technically adequate studies, MRPA had a sensitivity of 78% and a specificity of 99%.

**What is the value of digital subtraction angiography (DSA) in the diagnostic assessment of suspected PE in a pregnant woman? (Descriptive, Evidence Table E7).** There are no studies that evaluate the performance of DSA for the diagnosis of PE in pregnancy. In the general population, three studies have shown that a negative pulmonary angiogram is associated with a low frequency (0–1.6%) of recurrent PE (51–53). Although pulmonary angiography has traditionally been viewed as the reference standard in diagnosis of PE, a retrospective review of 20 discordant cases (20/226, prevalence 8.8%) found in the PIOPED II trial showed that DSA is less sensitive than CTPA in detection of emboli: DSA had 1 false-positive and 13 false-negatives, as compared with 2 false-negatives with CT (54). Four additional cases showed thrombus at angiography but were true-negative at CT, with presumed lysis of the clot in the interval between the two studies. The largest missed thrombus at DSA was subsegmental in eight patients, segmental in two patients, and lobar in three patients; at CT, the largest missed thrombus was subsegmental.

**What is the optimal imaging paradigm for suspected PE in a pregnant woman?** Direct evidence for the effectiveness of any published imaging paradigm does not exist. In coming to a recommendation, panel members reviewed the data from all preceding questions and formulated the algorithm (Figure 1) shown in the Executive Summary.

## Recommendations

**Recommendation 1.** In pregnant women with suspected PE, we suggest that D-dimer not be used to exclude PE (weak recommendation, very-low-quality evidence).

**Remarks.** This recommendation puts a high value on avoiding false negatives; it puts a lower value on avoidance of further diagnostic tests for the women with true negative results.

**Recommendation 2.** In pregnant women with suspected PE and signs and symptoms of DVT, we suggest performing bilateral CUS of lower extremities followed by anticoagulation treatment, if positive and further testing, if negative (weak recommendation, very-low-quality evidence).

**Remarks.** This recommendation puts a high value on avoidance of further work-up with radiation-associated tests. It places a lower value on cost and the potential benefit of a baseline comparison study of the pulmonary vasculature if the patient should represent with symptoms suggestive of PE.

**Recommendation 3.** In pregnant women with suspected PE and no signs and symptoms of DVT, we suggest performing studies of the pulmonary vasculature rather than CUS of the lower extremities (weak recommendation, very-low-quality evidence).

**Remarks.** This recommendation puts a high value on cost and cost-effectiveness. It places a lower value on avoidance of further work-up with radiation-associated procedures in the small fraction of women who have a DVT.

**Recommendation 4.** In pregnant women with suspected PE we recommend a CXR as the first radiation-associated procedure in the imaging work-up (strong recommendation, low-quality evidence).

**Remarks.** This recommendation puts a high value on minimizing radiation dose to the mother by using results of the CXR to triage between lung scintigraphy and CTPA.

**Recommendation 5.** In pregnant women with suspected PE and a normal CXR, we recommend lung scintigraphy as the next imaging test rather than CTPA (strong recommendation, low-quality evidence).

**Remarks.** This recommendation puts a high value on minimizing radiation dose to the mother. It puts a lower value on rapidity of the diagnostic test and the possibility of alternate diagnoses afforded by CTPA.

**Recommendation 6.** In pregnant women with suspected PE and a nondiagnostic  $\dot{V}/\dot{Q}$  scan, we suggest further diagnostic testing rather than clinical management alone (weak recommendation, low quality evidence). In patients with a nondiagnostic  $\dot{V}/\dot{Q}$  scan in whom a decision is made to further investigate, we recommend CTPA rather than DSA (strong recommendation, very-low-quality evidence).

**Remarks.** This recommendation puts a high value on diagnostic certainty given the potentially morbid consequences if PE is undiagnosed due to a nondiagnostic  $\dot{V}/\dot{Q}$  scan. The recommendation of CTPA over DSA places a high value on minimizing maternal radiation dose and potential procedural complications.

**Recommendation 7.** In pregnant women with suspected PE and an abnormal CXR, we suggest CTPA as the next imaging test rather than lung scintigraphy (weak recommendation, very-low-quality evidence).

**Remarks.** This recommendation puts a high value on achieving a diagnostic study, minimizing the time delay to a diagnosis, and enhancing the likelihood of finding an alternate diagnosis.

## DISCUSSION

Pulmonary embolism is an important and potentially fatal disease that is predisposed in pregnant women, with an estimated incidence of 10.6 per 100,000 (12); risk is highest during the postpartum period (2, 12). In addition to appropriate prophylaxis and therapy, prevention of maternal mortality from PE requires a high degree of clinical suspicion followed by a timely and accurate diagnostic approach. A multidisciplinary panel

including major medical stakeholders from five different societies (American Thoracic Society, Society of Thoracic Radiology, Society of Nuclear Medicine, American College of Obstetricians and Gynecologists, and American Association of Physicians in Medicine) participated in the development of this clinical practice guideline on the optimal work-up and imaging paradigm for pregnant patients with suspected PE.

One of the strengths of these guidelines is the transparent evidence-based approach with explicit description of the values that influenced the recommendations. The main weaknesses are the low quality and very limited amount of direct evidence pertaining to diagnostic test accuracy and patient-important outcomes in the pregnant population.

Prevalence of PE in pregnant women presenting with suspicious signs and symptoms ranges from 3 to 6% in recent clinical series (8, 9, 33). Additional research is needed to identify a combination of clinical factors that can better define the group at risk and, optimally, predict the probability of PE. Prospective studies needed to evaluate the role of D-dimer and cost-effectiveness of CUS in evaluation of PE in pregnancy are most likely to yield meaningful results when performed in concert with a clinical prediction rule. There are currently no high-quality studies evaluating accuracy of  $\dot{V}/\dot{Q}$  scan, CTPA, MRPA, or DSA in detection of PE in the pregnant population; the effect of pregnancy stage (trimester) on any diagnostic test's performance is unknown. Prospective management studies are required to validate the high negative predictive values of  $\dot{V}/\dot{Q}$  scan and CTPA reported in retrospective series (8, 33, 39).

Even in the face of low-quality evidence, the panel arrived at strong recommendations—implying that they should be followed in most situations—in three specific scenarios: performance of chest radiography as the first radiation-associated procedure; use of lung scintigraphy as the preferred test in the setting of a normal CXR; and if a decision is reached to further investigate, performance of CTPA rather than DSA in a pregnant woman with a nondiagnostic  $\dot{V}/\dot{Q}$  result. All of these recommendations resulted after consideration of the balance between desirable and undesirable effects of these tests.

As an independent test, CXR rarely allows for a confident alternate diagnosis; however, radiographic findings may occasionally confirm clinically suspected alternate diagnoses such as pulmonary edema. When used in combination, definitive  $\dot{V}/\dot{Q}$  results are achieved in more than 90% of pregnant women with suspected PE and a normal CXR, thereby obviating the need for more expensive and higher radiation dose studies. The strong recommendation that these two tests be performed early in the diagnostic algorithm reflects the high value placed on minimizing maternal radiation dose necessary to diagnose or exclude PE in the pregnant woman. As compared with DSA, CTPA is similarly associated with a lower maternal radiation dose (Table 4) as well as a lower risk for major procedural complications.

The risks of radiation exposure associated with diagnostic imaging in pregnancy is complicated by the presence of two at-risk individuals, the fetus and the mother. Although there is no consensus as to whether  $\dot{V}/\dot{Q}$  scans or CTPA delivers the lower fetal radiation dose, measured values for the two studies are low, roughly equivalent, and similar to the dose (0.5–1 mGy) absorbed by the fetus from naturally occurring background radiation during the 9-month gestational period (Table 4) (21, 55, 56). In contrast to the minimal fetal risk, the estimated risk for the mother is higher with breast and lung cancers considered most likely to account for radiation-induced cancer mortality (57). As compared with  $\dot{V}/\dot{Q}$  scan, CTPA is associated with a higher radiation dose to the mother: the calculated doses to breast and

lung tissue have been estimated to range from 10 to 60 mGy and 39.5 mGy, respectively with CTPA as compared with 0.98 to 1.07 mGy and 5.7 to 13.5 mGy, respectively with  $\dot{V}/\dot{Q}$  scan (58–62).

Based upon the currently accepted linear no-threshold model, a pregnant woman who undergoes a CTPA is predicted to have a higher lifetime risk of developing a radiation-induced cancer than if she had undergone a lower dose procedure such as lung scintigraphy. However, precise quantification of cancer risk associated with exposure to very low levels of ionizing radiation is currently not possible (57). Using the Biologic Effects of Ionizing Radiation (BEIR) VII risk models developed by the National Research Council (NRC) (57), Hurwitz and colleagues (63) calculated the lifetime relative risk of radiation-induced breast and lung cancer in a 25-year-old woman who undergoes a single CTPA study to be 1.011 and 1.022, respectively. Inherent in any risk estimate is considerable uncertainty arising from limitations in available epidemiologic data and in current understanding of radiation carcinogenesis (57). In their BEIR VII report, the NRC committee advises that specific estimates of lifetime assessed risk (LAR) be regarded with “healthy skepticism” with placement of more faith in a range of possible values; their derived subjective confidence intervals for specific LAR estimates cover at least an order for magnitude for most site-specific cancers with both under- and overestimation of risk considered possible (57, 64).

The benefits and risks of undergoing a diagnostic work-up should be discussed with the pregnant woman. The limitations and uncertainties of estimated risk of radiation-induced cancer should also be discussed and placed in the context of the well-understood expected clinical benefits of diagnostic work-up. The purpose of the informed consent process is to empower the woman to exercise her autonomy by providing her information about her condition; the medically reasonable alternatives for management; the clinical benefits and risks of each alternative to her, her fetal patient, and her future child; and the alternative of nonintervention with its benefits and risks. “Medically reasonable” means that evidence-based reasoning supports a reliable expectation that performing a technically possible intervention will result in a greater balance of clinical benefits over clinical harms (65). With sudden death of mother and fetus as the overriding risk, physicians are justified in recommending work-up in suspected cases of PE. However, given the lack of evidence documenting clear superiority of any one diagnostic test, the values and preferences of a patient and her physician likely will and should determine the final choice and sequence of tests performed.

If the decision is made to perform a study using ionizing radiation, care should always be taken to keep the radiation dose as low as reasonably achievable while maintaining the diagnostic quality of the exam. For CTPA, this would include adjusting the technical factors for the size of the mother (or using tube current modulation techniques) as well as limiting the dose to the fetus by limiting the scan length where possible and including use of dynamic collimation techniques when available. Dose reduction techniques for lung scintigraphy include using one half the usual administered activity of Technetium-99m (Tc-99m) macroaggregated albumin for the perfusion scan and increasing the scan time to achieve adequate counts. When possible, a Xenon-133 ventilation scan should be performed instead of a Tc-99m aerosol ventilation study, since the effective dose to the mother is lower. While some experts recommend omitting the ventilation scan, this may decrease the diagnostic accuracy of the study. Further dose reduction techniques include hydration to encourage frequent urinary voiding and reduction of fetal exposure.

To minimize nondiagnostic and repeat studies, CTPA protocols performed in pregnant women should be specifically adapted and optimized to account for known physiologic changes

such as increases in cardiac output and blood volume that will affect contrast medium dynamics and result in decreased pulmonary arterial opacification. Protocol optimization for the pregnant state includes automated bolus triggering, a high iodine flux achieved through high flow rate (4.5–6 ml/s) and/or high iodine concentration (350–400 mg I/ml), and clear breathing instructions to minimize possible Valsalva effects (66).

These guidelines were developed with the aim of allowing simple implementation and under the assumption that patients are stable and all studies are equally available. In real-life situations in which either the patient is unstable or some studies are not available on a timely basis, empiric initiation of therapy and alternate diagnostic strategies should be considered. For a patient in whom there is a high clinical suspicion of PE and a low risk of bleeding, anticoagulant therapy is recommended while awaiting the outcome of diagnostic tests (strong recommendation, low-quality evidence) (67). Two studies (68, 69), both performed in nonpregnant, emergency department (ED) patients diagnosed with PE ( $n = 161$  and  $400$ ), have reported an association between prompt diagnosis with early anticoagulation administered in ED and reduction of adverse outcomes including mortality. Although indirect, these data suggest the importance of a timely diagnostic work-up. Ultimately, the decision as to when and under what circumstances empiric therapy and/or an alternate diagnostic strategy (such as the selection of CTPA over  $\dot{V}/\dot{Q}$ ) should be undertaken rests within the purview of the treating physician, who needs to consider not only the available evidence but also specific patient characteristics and preferences and who operates under specific local conditions.

Adoption of this guideline's recommendations should also take into account local practices and expertise. Reporting of  $\dot{V}/\dot{Q}$  scan results is currently not standardized, with different criteria for categorization of findings in use and variable inclusion of the “very low probability” and “low probability” groups into either the nondiagnostic or “PE absent” categories (39, 70, 71). To optimize communication, guidelines from the Society of Nuclear Medicine recommend that in addition to a description of the lung scintigraphy findings, each  $\dot{V}/\dot{Q}$  report should also include a diagnostic category as well as an overall assessment of the likelihood of PE (38). Technically inadequate CTPA studies of pregnant women have been reported to occur in 6 to 36% of cases, with suboptimal vascular opacification and respiratory motion artifact as the most frequently cited causes (34, 39–41). At sites with high rates of inadequate CTPA studies,  $\dot{V}/\dot{Q}$  scan may be a better alternative even in women with abnormal CXRs. Repeat CTPA in a pregnant woman who has already undergone one nondiagnostic study should be undertaken with caution unless review of the prior study reveals a technical opportunity for improvement that can increase the likelihood of a diagnostic repeat study.

The recommendations presented in these guidelines are based upon the currently available evidence. Availability of new clinical research data and development and dissemination of new technologies will necessitate a revision and update.

This official ATS/STR Guideline was prepared by the ad hoc subcommittee on Pulmonary Embolism in Pregnancy of the Pulmonary Circulation Assembly.

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