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# Diagnosis of Pulmonary Embolism During Pregnancy

## A Multicenter Prospective Management Outcome Study

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**Background:** Data on the optimal diagnostic management of pregnant women with suspected pulmonary embolism (PE) are limited, and guidelines provide inconsistent recommendations on use of diagnostic tests.

**Objective:** To prospectively validate a diagnostic strategy in pregnant women with suspected PE.

**Design:** Multicenter, multinational, prospective diagnostic management outcome study involving pretest clinical probability assessment, high-sensitivity D-dimer testing, bilateral lower limb compression ultrasonography (CUS), and computed tomography pulmonary angiography (CTPA). (ClinicalTrials.gov: NCT00740454)

**Setting:** 11 centers in France and Switzerland between August 2008 and July 2016.

**Patients:** Pregnant women with clinically suspected PE in emergency departments.

**Intervention:** Pulmonary embolism was excluded in patients with a low or intermediate pretest clinical probability and a negative D-dimer result. All others underwent lower limb CUS and, if results were negative, CTPA. A ventilation–perfusion (V/Q) scan was done if CTPA results were inconclusive. Pulmonary embolism was excluded if results of the diagnostic work-up were negative, and untreated pregnant women had clinical follow-up at 3 months.

**Measurements:** The primary outcome was the rate of adjudicated venous thromboembolic events during the 3-month follow-up.

**Results:** 441 women were assessed for eligibility, and 395 were included in the study. Among these, PE was diagnosed in 28 (7.1%) (proximal deep venous thrombosis found on ultrasound [*n* = 7], positive CTPA result [*n* = 19], and high-probability V/Q scan [*n* = 2]) and excluded in 367 (clinical probability and negative D-dimer result [*n* = 46], negative CTPA result [*n* = 290], normal or low-probability V/Q scan [*n* = 17], and other reason [*n* = 14]). Twenty-two women received extended anticoagulation during follow-up, mainly for previous venous thromboembolic disease. The rate of symptomatic venous thromboembolic events was 0.0% (95% CI, 0.0% to 1.0%) among untreated women after exclusion of PE on the basis of negative results on the diagnostic work-up.

**Limitation:** There were several protocol deviations, reflecting the difficulty of performing studies in pregnant women with suspected PE.

**Conclusion:** A diagnostic strategy based on assessment of clinical probability, D-dimer measurement, CUS, and CTPA can safely rule out PE in pregnant women.

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* For members of the CT-PE-Pregnancy Group, see the **Appendix** (available at Annals.org).

Pulmonary embolism (PE) is among the most common causes of maternal death in developed countries (1, 2). A potential explanation, besides the fact that pregnancy is associated with an increased risk for venous thromboembolism (VTE), is that diagnosing PE is particularly challenging during pregnancy. Pregnant women often have symptoms and signs suggestive of PE, such as shortness of breath or tachycardia (3). Evidence to guide clinicians on how to manage women with suspected PE is limited (4, 5). Because no prospective diagnostic management study has been published, clinical practice guidelines provide highly variable recommendations (5–9).

Use of conventional diagnostic algorithms for PE is limited by several factors. Pregnant women were excluded from studies that derived and validated models assessing pretest clinical probability of PE, and no specific tool to assess pretest probability is available in this setting (7, 10). In the nonpregnant population, the D-dimer test, a simple, noninvasive, and inexpensive blood test, may be used to rule out PE in around 30% of outpatients who do not have a high pretest clinical probability (11–14). The lack of a pretest probability assessment tool and the lack of prospective data confirming the safety of ruling out PE on the basis of a negative D-dimer result have limited the adoption of the D-dimer test in this setting. Moreover, D-dimer levels increase during pregnancy, limiting the chance of a negative result, although the exact yield of D-dimer for the diagnosis of VTE during pregnancy has never been formally evaluated (15).

Given the limitations of noninvasive testing, most pregnant women with suspected PE require chest im-

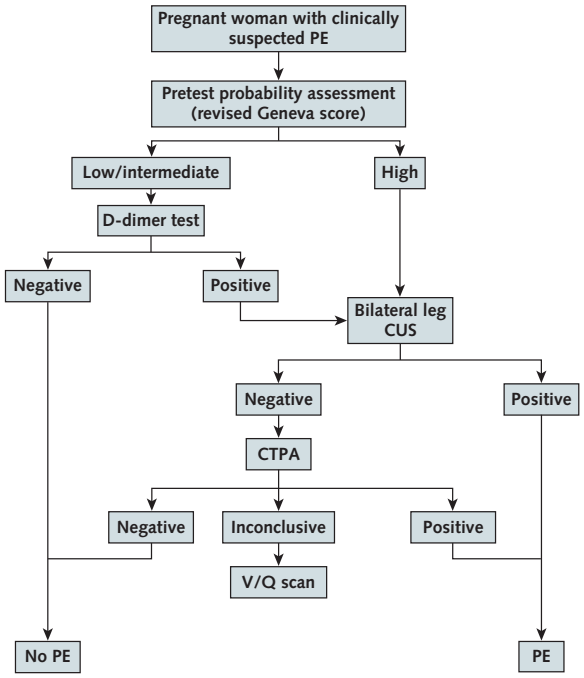
**See also:**

Editorial comment . . . . . 1

aging tests, either a ventilation–perfusion (V/Q) lung scan or computed tomography pulmonary angiography (CTPA). Which to use during pregnancy has been a matter of debate, mainly due to concerns about the consequences of radiation for the mother and the fetus (16, 17). However, scientific societies and experts agree that the risks associated with either test are much lower than the potential risks of inappropriate or incomplete diagnostic management, such as death due to undiagnosed PE or bleeding and long-term management consequences of misdiagnosed PE (9, 18–20). The rate of inconclusive test results leading to further testing is also a concern, with some retrospective studies suggesting that the rate of inconclusive CTPA results is much higher during pregnancy (21, 22). Use of bilateral lower limb venous compression ultrasonography (CUS) before chest imaging has been advocated. The finding of proximal deep venous thrombosis (DVT) is highly suggestive of PE, allowing for confirmation of the diagnosis without the need for additional chest imaging or anticoagulant treatment (23). However, others have raised concerns over the limited yield of CUS in the absence of DVT symptoms and its potentially lower accuracy during pregnancy (16).

To address these knowledge gaps, we conducted a prospective diagnostic management outcome study for diagnosis of PE in pregnant women. We evaluated a diagnostic algorithm that included an assessment of pretest clinical probability using the revised Geneva score, a highly sensitive D-dimer test, bilateral CUS, CTPA, and a V/Q scan if results of CTPA were inconclusive (Figure 1).

***Figure 1.*** Diagnostic algorithm used in the study.




CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; PE = pulmonary embolism; V/Q = ventilation–perfusion.

## METHODS

### Study Population

We conducted a multicenter, multinational, prospective diagnostic management outcome study. We screened outpatient pregnant women presenting at 1 of the participating centers with clinically suspected PE, defined as acute onset of new or worsening shortness of breath or chest pain without another obvious cause. Exclusion criteria were age less than 18 years, allergy to iodinated contrast agent, impaired renal function (defined as creatinine clearance <30 mL/min based on the Cockcroft–Gault formula), diagnosis before presentation, indication for or current receipt of full-dose anticoagulation, and inaccessibility for follow-up. The study was performed in 2 countries (France and Switzerland), and 11 centers actively enrolled patients. The study was approved by the ethics committee according to legislation at each study site, and written informed consent was obtained from all participants.

### Diagnostic Work-up

Pretest probability of PE was determined using the revised Geneva score. A D-dimer test was performed in all women by using the highly sensitive Vidas assay (bioMérieux). Pulmonary embolism was excluded in women who had low or intermediate pretest probability and a negative D-dimer result (<500 μg/L). Women who had high pretest probability or a positive D-dimer result underwent bilateral CUS. The test was performed in a standard manner, with B-mode ultrasonography in transverse view and compression of the deep veins of the lower limbs (including the common femoral, femoral, popliteal, peroneal, and posterior tibial veins) along their whole length in the thigh and calf. We used the commonly accepted diagnostic criterion for DVT of lack of compressibility of a deep vein. When proximal DVT (popliteal vein or above) was found, PE was considered to be confirmed and no further testing was done.

Women with a negative result on CUS underwent CTPA. The protocol for CTPA consisted of an evaluation of the pulmonary arteries up to and including the subsegmental vessels. Patients were examined while holding their breath or breathing shallowly, depending on the degree of dyspnea. Pulmonary embolism was considered to be present if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material. Only multidetector CT machines were used. The acquisition parameters for CTPA were injection of a total volume of 100 mL of nonionic contrast material (iodine concentration, 300 to 350 mg/mL) with a power injector at 3 to 5 mL/s; imaging 9 to 20 seconds after initiation of the contrast material injection; scanning performed at 1.0 to 1.3 mm per section, with a pitch of 1.25 to 1.75, 120 kV, and 115 to 260 mA; and reconstruction of images at 0.6- to 0.8-mm intervals. If results of CTPA were inconclusive, a V/Q lung

scan was performed, using 6 planar views and interpretation according to the PIOPED (Prospective Investigation Of Pulmonary Embolism Diagnosis) criteria. The complete diagnostic algorithm is depicted in Figure 1.

### Follow-up

Patients with negative results on the diagnostic work-up were considered to not have PE, did not receive anticoagulant treatment, and had 3 months of clinical follow-up. They were instructed to contact the study team in case of new or worsening symptoms and were interviewed by telephone by the study coordinators at the end of follow-up using a standardized questionnaire. Whenever a possible event was disclosed, the clinical history, results of diagnostic tests, and clinic or admission reports were collected for adjudication. A 3-member independent adjudication committee reviewed all suspected VTE events, with blinding to the initial diagnostic work-up. Adjudication was based on full consensus.

### Outcomes

The primary outcome was risk for adjudicated VTE events during the 3-month follow-up in women who did not receive anticoagulant therapy on the basis of negative results on the initial work-up. We calculated 95% CIs based on the Wilson score method without continuity correction (24) using an online calculator (25).

### Sample Size Estimation

For the diagnostic strategy to be deemed safe, we determined a priori that the upper limit of the 95% CI around the estimate of 3-month VTE risk should not be higher than 3.0%. Hypothesizing a 5% prevalence of PE and a 1.5% 3-month thromboembolic risk after normal results on CTPA, we concluded that a sample of 300 patients would allow confirmation of the safety of the diagnostic strategy.

### Role of the Funding Source

The funding sources had no role in the study design, interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

## RESULTS

Between August 2008 and July 2016, 441 pregnant women were screened. Seventeen declined to participate; 11 were unable to provide consent; 9 had testing for PE before being approached; 5 were allergic to contrast media; 1 was receiving long-term, full-dose anticoagulant treatment; 2 withdrew consent during the study; and 1 was not pregnant, leaving 395 who were included in the study. Characteristics of the included women are presented in Table 1. Seventeen were receiving prophylactic anticoagulation at inclusion, mainly for a previous VTE. The study flow chart is shown in Figure 2.

Pretest probability was low in 192 women (48.6%), intermediate in 200 (50.6%), and high in 3 (0.8%). Among the 392 women who did not have high pretest probability, 46 (11.7%) had a negative D-dimer result, 341 (87%) had a positive result, and 5 (1.3%) had no D-dimer testing. The proportion of negative D-dimer results decreased with increasing gestational age (21 of 83 [25.3%] during the first trimester, 19 of 170 [11.1%] during the second trimester, and 6 of 142 [4.2%] during the third trimester). Of note, 11 women underwent CTPA despite a negative D-dimer result; 10 had negative CTPA results, and 1 had an inconclusive result followed by a normal V/Q scan. Of the 349 women with a positive D-dimer result, no D-dimer test, or high pretest probability, 321 (92%) had negative results on CUS, 7 (2.0%) had positive results, and 21 (6%) did not have CUS. Of the 342 patients who had a negative result or did not undergo CUS, 290 (84.8%) had negative results on CTPA, 19 (5.6%) had positive results, 23 (6.7%) had inconclusive results, and 10 (2.9%) did not have CTPA. Of the 33 women who had inconclusive results or did not undergo CTPA, PE was confirmed on the basis of a high-probability V/Q lung scan in 2 (6.1%), was excluded by a V/Q lung scan in 17 (51.5%), and was excluded without further testing in 14 (42.4%). Overall, PE was diagnosed in 28 (7.1%) women. The respective contributions of the diagnostic tests are summarized in Table 2.

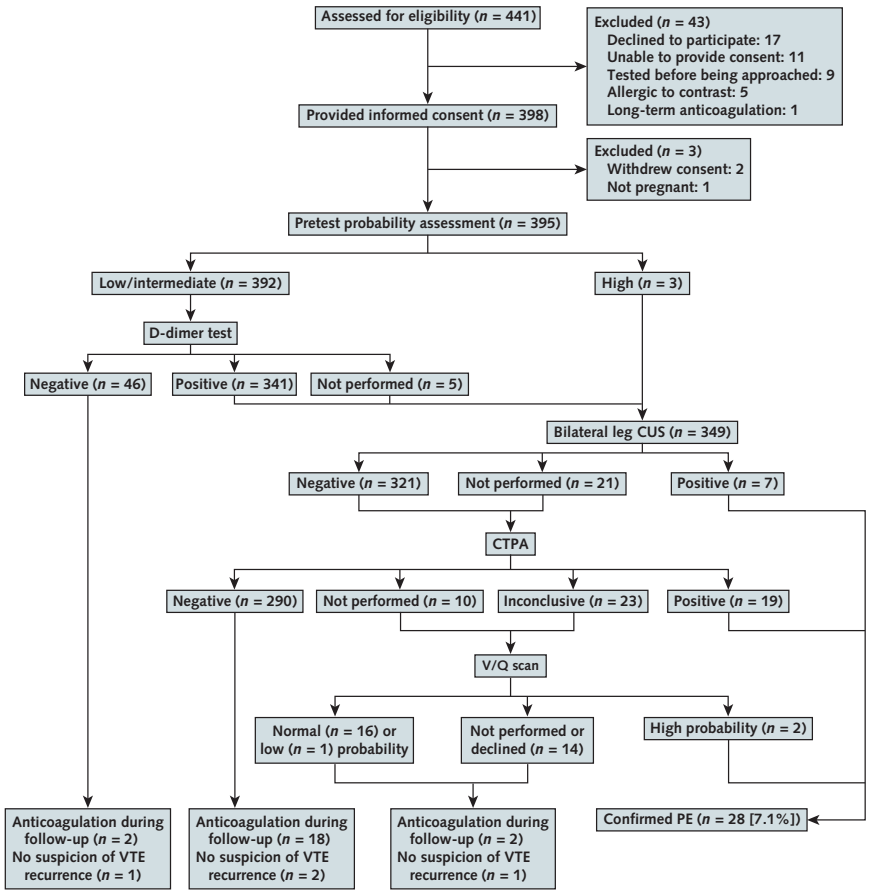
During follow-up, of the 367 women in whom PE was ruled out, 22 received anticoagulant therapy, mainly prophylactic anticoagulation in the setting of a prior VTE event ($n$ = 17); 3 started prophylactic anticoagulation during follow-up (for preeclampsia [$n$ = 2] or ovarian hyperstimulation syndrome [$n$ = 1]); and 2 received therapeutic anticoagulation after diagnosis of DVT in the calf ($n$ = 1) or an upper extremity ($n$ = 1) at the initial work-up. Four women were investigated for suspected VTE during follow-up (PE [$n$ = 3] or DVT [$n$ = 1]). All patients with suspected VTE had negative results on diagnostic testing, and none were adjudicated as having confirmed events. No deaths occurred during follow-up, and no patient was lost to follow-up. Therefore, in the intention-to-

***Table 1.*** Characteristics of Included Patients*

| Characteristic | Patients ($n$ = 395) |
|---|---|
| Median age (IQR), *y* | 31 (27–36) |
| Trimester of pregnancy, *n (%)* | |
| First | 83 (21.0) |
| Second | 170 (43.0) |
| Third | 142 (35.9) |
| Mean BMI (SD), *kg/m²* | 25.9 (5.5) |
| Personal history of VTE, *n (%)* | 29 (7.3) |
| Family history of VTE, *n (%)* | 45 (11.4) |
| Active cancer, *n (%)* | 0 (0) |
| Surgery in previous month, *n (%)* | 4 (1.0) |
| Bedridden for >72 h during past 4 wk, *n (%)* | 34 (8.6) |
| Travel for >6 h, *n (%)* | 15 (3.8) |
| Chest pain, *n (%)* | 260 (65.8) |
| Dyspnea, *n (%)* | 292 (73.9) |
| Syncope/lipothymia, *n (%)* | 59 (14.9) |
| Hemoptysis, *n (%)* | 14 (3.5) |
| Clinical signs or symptoms of DVT, *n (%)* | 57 (14.4) |
| Mean heart rate (SD), *beats/min* | 91 (17) |
| Mean $SaO_2$ (SD), *%* | 98.0 (1.8) |

BMI = body mass index; DVT = deep venous thrombosis; IQR = interquartile range; VTE = venous thromboembolism.
* Percentages may not sum to 100 due to rounding.

***Figure 2.*** Study flow chart: intention-to-diagnose analysis.




Three-month VTE risk among patients who did not receive anticoagulant treatment after negative results on the work-up was 0.0% (CI, 0.0% to 1.0%). CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; PE = pulmonary embolism; V/Q = ventilation–perfusion; VTE = venous thromboembolism.

diagnose analysis, thromboembolic risk at 3 months was 0.0% (95% CI, 0.0% to 1.0%). A sensitivity analysis that excluded 22 women who received prophylactic or therapeutic anticoagulation during follow-up had similar results, with a 3-month thromboembolic risk of 0.0% (CI, 0.0% to 1.1%).

### Per Protocol Analysis

We also conducted a per protocol analysis that excluded women with protocol deviations. Thirty-eight (9.6%) women had protocol deviations (no D-dimer test [*n* = 5], no CUS [*n* = 20], no CTPA [*n* = 8], and no V/Q scan after an inconclusive result on CTPA [*n* = 5]), leaving 357 women with suspected PE who had the complete diagnostic work-up and were included in the per protocol analysis. Pulmonary embolism was diagnosed in 24 of these women (6.7%). Of the remaining 333 women, 20 received prophylactic or therapeutic anticoagulation during follow-up. The 3-month risk for VTE in women not receiving anticoagulant therapy was 0.0% (CI, 0.0% to 1.2%) (Figure 3).

### Sensitivity Analysis

We performed sensitivity analyses to account for the 22 patients who received prophylactic anticoagulation. Under the assumption that 4, 5, or 10 VTEs would have occurred in these 22 patients had they not received anticoagulation, the upper 95% confidence bound for the 3-month thromboembolic risk was 2.8%, 3.1%, or 4.9%, respectively.

## DISCUSSION

In pregnant women with suspected PE, a diagnostic strategy involving assessment of pretest clinical probability, D-dimer measurement, bilateral leg CUS, and CTPA can safely rule out the disease, with a 3-month thromboembolic rate of 0.0% (CI, 0.0% to 1.0%). This meets the criteria recently proposed by the International Society on Thrombosis and Haemostasis for confirming the safety of VTE diagnostic strategies (26).

Several aspects of our study deserve comment. The proportion of patients with confirmed PE (7.1%) was

lower than that in the nonpregnant population in Europe (currently around 15% to 20%). However, this is in line with findings of previous retrospective studies among pregnant women. In a retrospective study by Chan and colleagues that used a V/Q-based algorithm, a 2% prevalence was reported in pregnant women with suspected PE (27).

Guidelines on the diagnostic management of women with suspected PE have been inconsistent in many respects, mainly due to the lack of prospective studies in this population (4, 5). Our study provides new insights on the role of the various diagnostic tests that may be used.

We used the revised Geneva score for assessment of pretest clinical probability (23). This clinical decision rule was derived and validated in a nonpregnant population and may not be optimal for use in pregnant women given some of its components, such as age older than 65 years, surgery in the previous month, or active cancer. However, no pretest probability assessment tool is available specifically for pregnant women with suspected PE (5). Therefore, we elected not to change the score composition or thresholds at this stage. Tailoring the Geneva score to pregnant women or deriving a specific rule for them could not be safely done a priori but will be feasible in the future using data from the present study. Nevertheless, the score was able to stratify women into 3 groups with increasing prevalence of PE (7 of 192 [3.6%] in the low–pretest probability group, 18 of 200 [9.0%] in the intermediate-probability group, and 3 of 3 [100%] in the high-probability group).

Guidelines and recent studies have been discrepant with regard to use of the D-dimer test during pregnancy (28, 29). Our study provides new data in this field. Although the subgroup of women with a negative D-dimer result was small, our study suggests that a negative D-dimer result combined with low or intermediate pretest probability can safely rule out PE during pregnancy, as in nonpregnant patients. Of note, the proportion of women in whom PE could be ruled out on the basis of a negative D-dimer result was clinically significant in this setting given that chest imaging could be avoided in 11.6% of the included women. Also notable was that the proportion of negative D-dimer results decreased with increasing gestational age, but this remained significant and clinically useful at least during the first and second trimesters (25% and 11%, respectively).

Use of bilateral CUS, with the goal of avoiding chest imaging in patients with proximal DVT, has been advocated in practice guidelines (6, 8). In our study, the yield of bilateral CUS was low (proximal DVT was confirmed in 7 of 395 [1.8%] tested patients). As in nonpregnant patients, the rate of proximal DVT detection was higher in women with suspected PE and signs or symptoms of DVT (5 of 57 [8.8%]) but remained relatively low even in this setting, calling into question the cost-effectiveness of this test. Of note, the sensitivity of CUS for diagnosis of PE was lower than in nonpregnant patients: 25% (7 of 28) of women with PE had a positive CUS result compared with the 41% sensitivity recently reported in a systematic review among nonpregnant patients with suspected PE (30). Therefore, in pregnant patients, it is especially important that a negative CUS result does not lead clinicians to stop investigations in the setting of the diagnostic work-up for suspected PE.

One of the most debated questions is whether a V/Q scan should be preferred over CTPA for diagnosis of PE during pregnancy, given concerns about the effects of radiation on the mother's breasts. Although our study did not address this question, we validated a CTPA-based algorithm in pregnant women given that such a prospective validation was lacking and the limited availability of the V/Q scan has led to widespread use of CTPA during pregnancy in many centers, despite the lack of thorough knowledge about its performance and safety in pregnant women. Another criticism about CTPA has been the potentially higher rate of inconclusive results reported in retrospective cohort studies (21, 31–33). The commonly postulated mechanism for this is modifications in blood volume and flow velocity during advanced pregnancy that are secondary to the highly modified hemodynamics associated with pregnancy. However, this finding was not confirmed in a recent systematic review that reported similar rates (approximately 12%) of inconclusive results among pregnant women having a V/Q scan or CTPA (34). In our study, the rate of inconclusive CTPA results was less than 10%, which is in line with the results of the recent review.

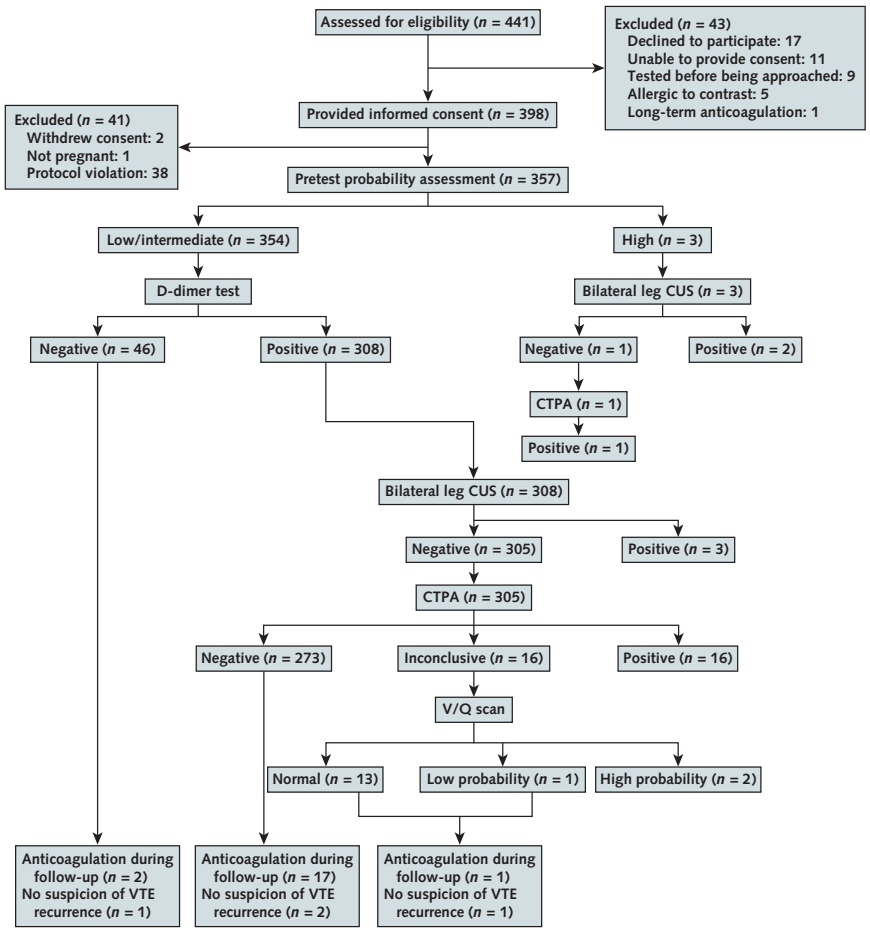
Strengths of our study include its prospective design. To our knowledge, with the exception of 1 meeting abstract presentation on an ongoing study (35), no prospective diagnostic management study of diagnosis of PE in pregnancy has been published. We found only 1 other trial using CTPA during pregnancy, which is ongoing (36). Other strengths of our study are that none of the included patients were lost to follow-up

***Table 2.*** Diagnostic Contributions of Tests in the Initial Work-up

| Variable | Patients (*n* = 395), *n* (%) |
|---|---|
| **PE diagnosed** | 28 (7.1) |
| Low or intermediate clinical probability | |
| Proximal DVT on ultrasonography | 5 (17.9) |
| Positive results on CTPA | 18 (64.3) |
| Inconclusive results on CTPA and high-probability V/Q scan | 2 (7.1) |
| High clinical probability | |
| Proximal DVT on ultrasonography | 2 (7.1) |
| Positive results on CTPA | 1 (3.6) |
| **PE ruled out on the basis of low or intermediate clinical probability** | 367 (92.9) |
| Negative D-dimer result | 46 (11.6) |
| Negative results on CTPA | 290 (73.4) |
| Inconclusive results on CTPA and normal or low-probability V/Q scan | 17 (4.3) |
| Other | 14 (3.5) |

CTPA = computed tomography pulmonary angiography; DVT = deep venous thrombosis; PE = pulmonary embolism; V/Q = ventilation–perfusion.

***Figure 3.*** Study flow chart: per protocol analysis.




Three-month VTE risk among patients who did not receive anticoagulant treatment after negative results on the work-up was 0.0% (CI, 0.0% to 1.2%). CTPA = computed tomography pulmonary angiography; CUS = compression ultrasonography; V/Q = ventilation–perfusion; VTE = venous thromboembolism.

and all suspected outcome events during follow-up were independently adjudicated.

Our study has limitations that deserve comment. The sample was small; however, the study was powered to assess the diagnostic safety of the algorithm. Nearly 10% of patients had protocol deviations, reflecting the difficulty of performing a complete diagnostic work-up during pregnancy. However, this is a low rate of deviations in this patient population. In a study by Roy and colleagues on the appropriateness of diagnostic management of PE in the emergency department, the rate of inappropriate management was as high as 69% among pregnant women, and pregnancy was by far the strongest predictor of inappropriate management (37). Although use of therapeutic anticoagulation was an exclusion criterion for the study, we did not exclude women receiving prophylactic anticoagulation because this is a common clinical scenario. Moreover, some women developed conditions during follow-up that required extended thromboprophylaxis. As a result, 6% of patients were receiving thromboprophylaxis during follow-up, which may have affected our results. However, a prophylactic dose of anticoagulants is unlikely to be sufficient to prevent a recurrent event if PE is missed by the diagnostic strategy at presentation. To account for the fact that some of these women might have developed VTE during follow-up had they not received anticoagulation, we conducted a sensitivity analysis showing that the upper limit of the 95% CI would still be less than 3%, even if 4 out of 22 women (18%) had presented with VTE.

In summary, a diagnostic algorithm involving sequential assessment of pretest clinical probability based on the Geneva score, D-dimer measurement, lower limb CUS, CTPA, and a V/Q scan safely rules out PE in pregnant women. The yield of D-dimer measurement is high enough to suggest its use for this indication. The contribution of systematic CUS seems limited, but it could still be used when a high value is placed on avoiding radiation. Using CTPA as the main imaging

test is a safe option in pregnant women with suspected PE, and the rate of inconclusive results is lower than previously reported and expected. Future research should focus on increasing the yield of noninvasive testing, such as by developing a specific clinical decision rule for suspected PE during pregnancy or using pregnancy-adapted D-dimer cutoff values.

From Geneva University Hospitals, Geneva, Switzerland (M.R., H.R., O.T.R., P.P.); Centre Hospitalier de Toulon, Toulon, France (A.E.); Université Paris Descartes, Sorbonne Paris Cité, and Hôpital Européen Georges Pompidou, Paris, France (O.S.); INSERM UMR S 1140, Paris, F-CRIN INNOVTE, Saint-Etienne, and Université de Brest, Brest, France (E.L.); Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France (J.S.); Centre Hospitalier d'Argenteuil, Argenteuil, France (C.L.); Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (J.C.); Bern University Hospital, University of Bern, Bern, Switzerland (D.A.); University Hospital of Angers, Angers, France (P.R.); INSERM U1059, University of Lyon, and University Hospital, Saint-Etienne, France (C.C.); and Université de Brest, Brest, France, and Ottawa Health Research Institute, Ottawa, Ontario, Canada (G.L.).

**Note:** All authors had access to all of the data in the study, read and approved the final manuscript, and were responsible for the decision to submit it for publication.

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**Reproducible Research Statement:** *Study protocol and statistical code:* Available from Dr. Righini (e-mail, Marc.Righini@hcuge.ch). *Data set:* Not available; however, eligible researchers who want to propose their own analyses may contact Dr. Righini.

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