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Review Article

Guidance for the diagnosis of pulmonary embolism during pregnancy: Consensus and controversies

Tony Wan [a], Leslie Skeith [a], Alan Karovitch [b], Marc Rodger [a], Grégoire Le Gal [a,*]

[a] Division of Hematology, Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada
[b] Division of General Internal Medicine, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

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ABSTRACT

Pulmonary embolism (PE) is one of the leading causes of maternal mortality despite a low incidence of PE during pregnancy. Several challenges surround the diagnosis of PE in pregnant women and the existing clinical guidelines provide weak recommendations on selecting the appropriate investigations for suspected PE in pregnancy. The purpose of this narrative review is to compare and contrast the recommendations of current clinical guidelines and review the evidence underpinning the recommendations on the evaluation of suspected PE in pregnancy. Consensus and controversies, knowledge gaps and areas requiring further research will be highlighted.

Contents

1. Introduction . . . 23
2. Methods . . . 24
3. Results and discussion . . . 24
   3.1. Clinical prediction rule . . . 24
   3.2. D-dimer . . . 25
   3.3. Leg vein imaging . . . 26
   3.4. Chest radiography . . . 26
   3.5. Ventilation perfusion scan and computed tomography pulmonary angiography . . . 26
4. Conclusion . . . 27
References . . . 27

1. Introduction

Pulmonary embolism (PE) is associated with significant mortality in the pregnant population [1]. PE remains the leading cause of maternal mortality in some developed countries despite ongoing research on the diagnosis and management of PE [2,3]. In Canada, the incidence of PE is 5.4 cases per 10,000 pregnancies [4]. The diagnosis of PE in pregnancy is challenging; physiological changes in pregnancy can overlap with clinical manifestations of venous thromboembolism (VTE) and the hyperdynamic circulation in pregnancy can influence the accuracy of diagnostic imaging [5,6]. Research on the diagnosis of PE has traditionally excluded pregnant women [7]. A major barrier to conducting clinical trials in the pregnant population is the difficulty in recruitment of participants [8]. A high-quality prospective study on the validation of

Abbreviations: PE, Pulmonary embolism; VTE, Venous thromboembolism; DVT, Deep vein thrombosis; CTPA, Computer tomography pulmonary embolism; V/Q, Ventilation perfusion; GTH, Working Group in Women's Health of the Society of Thrombosis and Haemostasis; RCOG, Royal College of Obstetrician and Gynecologist; ESC, European Society of Cardiology; SOGC, Society of Obstetricians and Gynecologist of Canada; ANZ, Australia and New Zealand; ASTH, Australasian Society of Thrombosis and Haemostasis; SOMANZ, Society of Obstetric Medicine of Australia and New Zealand; ATS/STR, American Thoracic Society/Society of Thoracic Radiology; EANM, European Association of Nuclear Medicine.

* Corresponding author at: The Ottawa Hospital, Centre for Practice-Changing Research, 501 Smyth Rd, Box 201A, Ottawa, ON K1H 8L6, Canada.
E-mail address: glegal@ohri.ca (G. Le Gal).

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Table 1
Guideline summary on clinical prediction rules for suspected PE in pregnancy.

Guideline	Recommendation
Working Group in Women's Health the Society of Thrombosis and Haemostasis (GTH 2016)	No recommendation
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"Clinicians should be aware that, at present, there is no evidence to support the use of pretest probability assessment in the management of acute VTE in pregnancy." (Grade A recommendation)
European Society of Cardiology (ESC 2014)	No recommendation
Society of Obstetricians and Gynecologist of Canada (SOGC 2014)	"Neither D-dimer alone nor clinical prediction rules should be used to rule out VTE in pregnant women without objective testing." (Class D recommendation)
Australia and New Zealand Guidelines (ANZ), endorsed by ASTH & SOMANZ (2012)	No recommendation
American Thoracic Society/Society of Thoracic Radiology (ATS/STR 2011)	No recommendation
European Association of Nuclear Medicine (EANM 2009)	No recommendation

a clinical prediction rule or biomarker for PE in pregnancy would require a relatively large sample size because of the high rate of negative investigations and thus adequate recruitment would take years [9]. Therefore, the current guidelines mostly extrapolate from results in the non-pregnant population and rely on the few existing observational studies in pregnant women.

Recommendations from clinical practice guidelines often rely on expert opinions, which may contribute to significant practice variation across regions. Inconsistency across guidelines can lead to additional uncertainty for frontline healthcare providers. The purpose of this narrative review is to compare and contrast the recommendations of current clinical guidelines and review the current evidence behind the recommendations on the evaluation of suspected PE in pregnancy. Consensus and controversies, knowledge gaps and areas requiring further research will be highlighted.

2. Methods

A literature search was performed using PubMed to identify all the clinical guidelines that provide recommendations on the diagnosis of suspected PE in pregnancy. Clinical guidelines that were not available in English were excluded. A total of seven guidelines from different organizations and societies were identified. The current guidelines from the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH), the Royal College of Obstetrician and Gynecologist (RCOG), the European Society of Cardiology (ESC), the Society of Obstetricians and Gynecologist of Canada (SOGC), the Australia and New Zealand (ANZ) Guidelines endorsed by the Australasian Society of Thrombosis and Haemostasis (ASTH) and the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ); the American Thoracic Society/Society of Thoracic Radiology (ATS/STR) and the European Association of Nuclear Medicine (EANM) were reviewed and the recommendations specific to the diagnosis of PE in pregnancy were extracted and summarized (Tables 1–4). The relevant primary literature supporting the extracted recommendations were reviewed and incorporated into the discussion.

3. Results and discussion

Tables 1–4 summarize the recommendations regarding the use of clinical prediction rules (Table 1), D-Dimer (Table 2), leg veins ultrasonography (Table 3), and chest imaging (Table 4) in the diagnostic work-up of pregnant women with clinically suspected PE.

3.1. Clinical prediction rule

Clinical prediction rules to determine the pretest probability of PE, well established in the non-pregnant population, were derived from studies that excluded pregnant women. Furthermore, these clinical prediction rules have not been validated in pregnancy [7,10]. Some items in these prediction rules, such as active malignancy or age > 65 years, are less relevant in the pregnant population. The specificity of the Wells criteria may be lower in pregnancy because tachycardia and lower limb edema are common findings in normal pregnancy [11]. In addition, the likelihood of an "alternative diagnosis to PE" is more difficult to assess [11]. The RCOG and the SOGC guidelines recommend against the use of clinical prediction rules to evaluate VTE during pregnancy while other guidelines do not provide any recommendations [11,12] (Table 1). The lack of high quality evidence is apparent as both guidelines rely on two small retrospective studies to support their weak recommendations. O'Connor et al. conducted a study that included 103 pregnant or post-partum women who were referred for computer tomography pulmonary angiography (CTPA) to evaluate for suspected PE in a single tertiary maternity institute [13]. They found that none of the women with a retrospectively assigned modified Wells score < 6 had a PE on CTPA, resulting in a negative predictive value of 100% (95% confidence interval not provided) [13]. Cutt et al. published a similar retrospective study that included

Table 2
Guideline summary on D-dimer testing for suspected PE in pregnancy.

Guideline	Recommendation
Working Group in Women's Health the Society of Thrombosis and Haemostasis (GTH 2016)	"Using the conventional reference ranges of non-pregnant individuals, a normal D-dimer test excludes VTE with the same likelihood in pregnant women."
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"D-dimer testing should not be performed in the investigation of acute VTE in pregnancy." (Grade D recommendation)
European Society of Cardiology (ESC 2014)	"D-dimer measurement may be performed in order to avoid unnecessary irradiation, as a negative result has a similar clinical significance as in non-pregnant patients." (Class IIb recommendation)
Society of Obstetricians and Gynecologist of Canada (SOGC 2014)	"Neither D-dimer alone nor clinical prediction rules should be used to rule out VTE in pregnant women without objective testing." (Class D recommendation)
Australia and New Zealand Guidelines (ANZ), endorsed by ASTH & SOMANZ (2012)	No recommendation
American Thoracic Society/Society of Thoracic Radiology (ATS/STR 2011)	"In pregnant women with suspected PE, we suggest that D-dimer not be used to exclude PE." (Weak recommendation)
European Association of Nuclear Medicine (EANM 2009)	No recommendation

Table 3
Guideline summary on the use of leg vein imaging for suspected PE in pregnancy.

Guideline	Recommendation
Working Group in Women's Health the Society of Thrombosis and Haemostasis (GTH 2016)	"In cases of clinically suspected PE, echocardiography and ultrasound examination of the lower extremities should be considered as initial imaging methods to substantiate the suspicion of PE and confirm the diagnosis of VTE, respectively."
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"In women with suspected PE who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasound confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue." (Grade C recommendation)
European Society of Cardiology (ESC 2014)	"Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal DVT confirms PE." (Class IIb recommendation)
Society of Obstetricians and Gynecologist of Canada (SOGC 2014)	No recommendation
Australia and New Zealand Guidelines (ANZ), endorsed by ASTH & SOMANZ (2012)	No recommendation
American Thoracic Society/Society of Thoracic Radiology (ATS/STR 2011)	"In pregnant women with suspected PE and signs and symptoms of DVT, we suggest performing bilateral venous compression ultrasound of lower extremities, following by anticoagulation treatment if positive and by further testing if negative." (Weak recommendation)
European Association of Nuclear Medicine (EANM 2009)	No recommendation

183 pregnant women with suspected PE who underwent ventilation perfusion (V/Q) scanning and found that all 107 women with a modified Wells score < 5 had a normal V/Q scan [9].

The paucity of evidence is reflected in the weak or absent guideline recommendations, with insufficient data to support the use of clinical prediction rules in the evaluation of suspected PE in pregnancy. Deriving and validating a clinical prediction rule for PE in pregnant women should be a focus for future research. Assessing the pretest probability is a crucial step in the assessment of patients with suspected PE, as it helps in reaching a diagnostic conclusion, in combination with the results of other diagnostic testing.

3.2. D-dimer

A normal D-dimer in combination with a non-high or unlikely pretest probability can safety rule out PE in the general population. However, the D-dimer test should not be used in patients with a high or likely pretest probability because the post-test probability of disease might be too high even in case of a negative D-dimer, resulting in false negative test results that may miss a PE [15]. Pregnant women were excluded from most of the relevant studies that established the use and limitation of D-dimer testing in the diagnosis of PE [16]. Controversy exists for the use of D-dimer testing during pregnancy among the published guidelines. The lack of a validated clinical prediction rule makes it challenging to properly interpret the D-dimer testing results in pregnant women with suspected PE. On the other hand, being able to safely exclude the disease without diagnostic imaging, which is associated with maternal and fetal radiation exposure, is highly appealing. The GTH and the ESC guidelines recommend that a normal D-dimer can be used to avoid unnecessary imaging investigations in pregnant women with suspected PE, while the RCOG, SOGC and ATS/STR guidelines recommend against the use of D-dimer to rule out PE in pregnancy [11,12,17,18,19] (Table 2). The ESC guideline grades their recommendation for using D-dimer testing as Class IIb, reflecting Level C evidence

Table 4
Guideline summary on V/Q scan and CTPA for suspected PE in pregnancy.

Guideline	Recommendation
Working Group in Women's Health the Society of Thrombosis and Haemostasis (GTH 2016)	"If lung scintigraphy is available, a low-dose perfusion scan is the preferred imaging technique to diagnose or exclude pregnancy-associated PE in women with normal chest X-ray (CXR) because this method exposes maternal breasts to less radiation than CTPA. If an initial CXR is abnormal or if lung scintigraphy is non-conclusive or not available, CTPA should be prioritized."
Royal College of Obstetrician and Gynecologist (RCOG 2015)	"In women with suspected PE without symptoms and signs of DVT, a V/Q lung scan or a CTPA should be performed." (Grade C recommendation) "When the CXR is abnormal and there is clinical suspicion of PE, CTPA should be performed in preference to a V/Q scan." (Grade D recommendation) "Alternative or repeat testing should be carried out where V/Q scan or CTPA is normal but the clinical suspicion of PE remains." (Grade C recommendation)
European Society of Cardiology (ESC 2014)	"Perfusion scintigraphy may be considered to rule out suspected PE in pregnant women with normal CXR." (Class IIb recommendation) "CTPA should be considered if the CXR is abnormal or if lung scintigraphy is not readily available." (Class IIa recommendation)
Society of Obstetricians and Gynecologist of Canada (SOGC 2014)	"For the diagnosis of PE, either V/Q scan or CTPA can be used." (Class A recommendation) "In pregnant women, a V/Q scan is the preferred test." (Class B recommendation)
Australia and New Zealand Guidelines (ANZ), endorsed by ASTH & SOMANZ (2012)	"V/Q scanning is the preferred investigation in pregnant or postpartum women with suspected PE who have a normal CXR." (Level 1 group consensus) "CTPA should be used in women with an abnormal CXR or where V/Q scanning is inconclusive or not available." (Level 1 group consensus)
American Thoracic Society/Society of Thoracic Radiology (ATS/STR 2011)	"In pregnant women with suspected PE and a normal CXR, we recommend lung scintigraphy as the next imaging test rather than CTPA." (Strong recommendation) "In pregnant women with suspected PE and an abnormal CXR, we suggest CTPA as the next imaging test rather than lung scintigraphy." (Weak recommendation)
European Association of Nuclear Medicine (EANM 2009)	"In pregnancy, particularly during the first trimester, a 2-day protocol starting with a perfusion-only scan followed if necessary by a second day ventilation study." (Grade C recommendation)

(expert opinion and/or small studies, retrospective studies, registries) and the GTH guideline does not grade their recommendation for using D-dimer testing. Indirect evidence from observational studies on using D-dimer to evaluate pregnant women with suspected deep vein thrombosis (DVT) reported a high negative predictive value suggesting that a negative D-dimer test is sufficient to safely exclude DVT [20,21]. In contrast, one small retrospective study that included 37 pregnant women with suspected PE who underwent both V/Q scan and D-dimer testing suggested that the sensitivity and specificity of D-dimer as a test for suspected PE were only 73% and 15%, respectively [22]. The result may have been influenced by selection bias as women who did not have D-dimer testing prior to the V/Q scan were excluded from the study population.

At this point, we believe that D-dimer testing should not be used to rule out PE in pregnancy for several reasons. First, data on the sensitivity and negative predictive value of D-dimer as a test for suspected PE in pregnancy is limited and inconsistent. Second, the lack of a clinical prediction rule in pregnancy is a major limitation of this strategy because a normal D-dimer in combination with a non-high pretest probability is required to rule out PE in the current diagnostic algorithm for the non-pregnant population. Third, D-dimer increases as normal pregnancy progresses and the appropriate cutoff value remains unclear. This highlights the need for prospective studies to evaluate the role of D-dimer testing in pregnant women with suspected PE.

3.3. Leg vein imaging

Compression ultrasound in combination with direct imaging and Doppler flow evaluation of the iliac veins is the test of choice in the diagnosis of DVT of the lower limb in pregnant women [23–25]. The rationale for performing leg vein imaging in pregnant women with suspected PE is that the confirmation of DVT leads to the same therapeutic management with anticoagulation as PE and avoids radiation exposure with diagnostic imaging for PE. Ultrasound is non-invasive and does not carry a radiation risk, in contrast to V/Q scan or CTPA, which are associated with maternal and fetal radiation exposure. Four guidelines recommend the use of lower limb ultrasound in pregnancy women with suspected PE but there are controversies on how to select the appropriate patients in order to optimize the diagnostic yield [12,17–19] (Table 3). The GTH and the ESC guidelines recommend bilateral lower limb ultrasound for all pregnant patients with suspected PE regardless of DVT symptoms [17,18]. However, the RCOG and ATS/STR guidelines recommend that lower limb ultrasound should only be performed if the clinical features of DVT are present [12,19]. The rationale for the latter approach is that the diagnostic yield of lower limb ultrasound is estimated to be low in the absence of DVT symptoms and routine ultrasound may delay diagnostic imaging for PE while adding unnecessary cost to the health care system. In fact, Cooper conducted a retrospective study of 158 pregnant women with suspected PE who had bilateral leg ultrasound and demonstrated that no DVT was detected in the absence of symptoms [26]. Bilateral lower limb ultrasound in pregnant women without symptoms of DVT can potentially lead to overdiagnosis because the rate of a false positive test is increased when the pretest probability is low. Therefore, routine ultrasound does not appear to be cost-effective but an economic analysis is not possible until more data on the rate of abnormal ultrasound is available in this population.

3.4. Chest radiography

Chest radiography is neither sensitive nor specific in detecting PE [27]. However, it remains important in the evaluation for PE as it can reveal other pathologies that may explain a patient's presenting symptoms [28]. Chest radiography is essential to accurately interpret abnormal V/Q scan findings [29]. The fetal radiation exposure from a single chest radiography is negligible and further minimized by abdominal shielding [30]. Most clinical guidelines include chest radiography as the initial imaging investigation in the diagnostic algorithm for pregnant women with suspected PE. Furthermore, five guidelines recommend preferential use of V/Q scan for pregnant women with suspected PE when the chest radiography is normal and they recommend the use of CTPA when the chest radiography is abnormal [12,17–19,31] (Table 4). According to the Revised PIOPED V/Q scan criteria, a normal chest radiograph is often required to classify the result into high probability, intermediate probability or low probability [32]. Therefore, any abnormality on the chest radiography will inevitably increase the likelihood of a nondiagnostic V/Q scan and favor the use of CTPA. In fact, a retrospective study showed that the frequency of nondiagnostic CTPA was five fold greater than V/Q scan in the subgroup of pregnant patients with a normal chest radiography [33]. However, this strategy of using chest radiograph to select patients for different diagnostic imaging has never been validated in prospective outcome studies.

3.5. Ventilation perfusion scan and computed tomography pulmonary angiography

CTPA has largely replaced V/Q scan as the diagnostic imaging of choice for PE in the non-pregnant population, however, the decision to order a CTPA or V/Q scan as the first line diagnostic imaging for pregnant women with suspected PE is a major topic of debate [5]. Issues regarding comparative accuracy of the tests, diagnostic yield and the implications of using a lower dose of IV contrast or radiopharmaceutical material remain unclear. Currently, most guidelines recommend the use of V/Q scan over CTPA and this is partly driven by the goal of minimizing maternal radiation exposure, instead of the superior diagnostic accuracy of the test [11,12,17]. Research suggests that the estimated lifetime attributable risk of cancer associated with computed tomography is greater in young women because radiosensitivity of the breast is higher at younger ages [34]. Some experts theorize that radiosensitivity of the breast is even higher during pregnancy because of breast tissue proliferation. While radiation exposure and the associated clinical consequences is an important consideration, our discussion will focus on the diagnostic characteristics and value of the two widely used imaging modalities for the diagnosis of PE.

The evidence for using CTPA or V/Q scan to exclude PE in pregnant women is limited because prospective data is scarce. A negative CTPA has a high negative predictive value for PE in pregnancy according to retrospective data [35,36]. Nijkeuter et al. published an abstract on a prospective study that measured the occurrence of symptomatic or fatal VTE at 3 month follow-up in 149 pregnant women with suspected PE who were investigated with CTPA, however the complete results are not published yet [37]. Although some participants had not completed the 3 month follow-up at the time of the abstract publication, the results appear promising as none of the pregnant women with a negative CTPA presented with VTE on follow-up so far [37].

Small retrospective studies looked at the clinical outcome of pregnant women with suspected PE who were investigated with V/Q scan and the results suggest that anticoagulation can be safely withheld if the V/Q scan is normal [7,38]. Studies by Balan et al. and Chan et al. found that all of the pregnant women with suspected PE who had a normal standard protocol V/Q scan and did not receive anticoagulation therapy, 52 in Balan's study and 104 in Chan's study, had no documented PE during the follow up period that ranged from 2 weeks to 108 months [7,38].

The V/Q scan protocol is often modified to minimize the fetal and maternal radiation exposure. The low dose perfusion scan is performed by using half of the standard radiopharmaceutical dose of technetium labeled macro-aggregated albumin while doubling the scan time in order to achieve the standard counts and multiple retrospective studies suggest that its performance in safely excluding PE in pregnant women appears to be comparable to the standard protocol V/Q scan [35,39,40].

Richard and colleagues conducted a retrospective study to evaluate if a perfusion scan alone with low radiopharmaceutical dose was sufficient to exclude PE during pregnancy; they found that 70 out of the 77 pregnant women had a normal perfusion scan and none of these women presented with VTE on follow-up [39]. In the other 7 pregnant women, 5 had a low probability scan and 2 had an intermediate probability scan [39]. The GTH guideline recommends a low dose perfusion scan without the ventilation study and the EANM guideline recommends a two-day protocol starting with a perfusion scan and then a ventilation study on the following day only if necessary [17,41] (Table 4). However, the two-day protocol is solely based on expert opinion from a committee in the European Association of Nuclear Medicine [41]. Neither of these diagnostics strategies has been prospectively validated in pregnant women with suspected PE.

V/Q scans have a higher proportion of nondiagnostic studies compared to CTPA in the non-pregnant population, which is one of the reasons why CTPA has become the diagnostic test of choice [42–44]. However, the performance of CTPA may be more affected by the physiological changes of pregnancy as four retrospective studies that compared the proportion of nondiagnostic CTPA to V/Q scans in pregnancy showed a favorable trend for V/Q scanning [6,33,35,45]. However, only one of the four studies demonstrated a statistically significant difference between the rate of nondiagnostic testing with V/Q scans and CTPA, 2.1% and 35.7% respectively [6]. Inadequate opacification of the pulmonary vasculature during CTPA is reported twice as often in pregnant patients as compared to non-pregnant patients [46]. Potential physiological explanations include increased plasma volume causing contrast medium dilution and hyperdynamic circulation of pregnancy resulting in the interruption of contrast bolus when the opacified blood from the superior vena cava is mixed with the unopacified blood from the inferior vena cava [6,46]. Reassuringly, a recent systematic review that included 22 studies with 2391 scans (1165 V/Q scan and 1226 CTPA) demonstrated that the pooled proportion of nondiagnostic studies in pregnancy is similar between V/Q scan and CTPA, 12.5% (95% CI 5.3–19.6) and 11.5% (95% CI 7.5–18.4), respectively [47].

A major limitation to the published studies on V/Q scan or CTPA in pregnancy is the retrospective design which is subjected to various forms of biases, such as information bias and selection bias. For instance, the outcome measure is often not obtainable because the researchers depend on the availability of the clinical documentation to identify management outcomes such as subsequent VTE at follow-up after the initial diagnostic imaging. One missed data point can significantly alter the results because the sample size of the relevant studies is small due to challenges in recruitment. Furthermore, selection bias is inevitable when studies do not recruit consecutive patients prospectively. Prospective studies on the diagnostic accuracy, yield and different imaging protocols for V/Q scan and CTPA are urgently needed.

Despite the uncertainties and controversies, diagnostic imaging should not be withheld or postponed in pregnant women with suspected PE because the consequences of missing or delaying the diagnosis of PE can be catastrophic. Empiric treatment is also problematic because it is associated with increased bleeding risk and other clinical implications, such as barrier to neuraxial analgesia and indication for antepartum VTE prophylaxis in future pregnancies, that outweigh the risks of radiation exposure associated with V/Q scan or CTPA. In summary, either V/Q scan or CTPA should be performed for all pregnant women with a clinical suspicion for PE.

4. Conclusion

PE is one of the leading causes of maternal mortality and high-quality research in the diagnosis of this treatable condition is essential. Current clinical practice guidelines are limited by a lack of direct evidence from studies that include pregnant women. The reliance on retrospective studies and expert opinion likely contributes to discrepancies seen between guideline recommendations and practice variation among clinicians. Hopefully, clinical practice guidelines can provide more clear directions in the future as research advances.

The need for high-quality research is obvious. Specifically, prospective studies on clinical prediction rules, D-dimer testing and diagnostic imaging are required urgently. A prospective outcome study on using CTPA to safety exclude PE in pregnancy has been recently completed in the Netherlands [37]. In France, a prospective study on a diagnostic algorithm using D-dimer, leg ultrasound and CTPA is close to completion (NCT00771303). The Artemis Study is a prospective trial assessing a diagnostic algorithm that consists of a modified version of Wells criteria, D-dimer testing, leg ultrasound and CTPA and it will start recruitment soon (NTR5913). Another prospective study evaluating a diagnostic algorithm with clinical risk factors, leg ultrasound and V/Q scan was started in Canada approximately 10 years ago and hopefully the results will be available soon. With additional research, development and validation of pregnancy-specific diagnostic algorithms there can hopefully be an improvement in the care of pregnant patients with suspected PE.

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