The diagnostic management of suspected pulmonary embolism in special patient populations

Stals, M.A.M.

4

Non-invasive diagnostic work-up for suspected acute pulmonary embolism during pregnancy: a systematic review and meta-analysis of individual patient data

Milou A.M. Stals, Thomas Moumneh, Fionnuala Ni Ainle, Drahomir Aujesky, Thomas van Bemmel, Laurent Bertoletti, Ingrid M. Bistervels, Céline Chauleur, Francis Couturaud, Yordi P.A. van Dooren, Antoine Elias, Laura M. Faber, Catherine Le Gall, Herman M.A. Hofstee, Tom van der Hulle, Marieke J.H.A. Kruip, Maxime Maignan, Albert T.A. Mairuhu, Saskia Middeldorp, Emmanuelle Le Moigne, Mathilde Nijkeuter, Liselotte M. van der Pol, Helia Robert-Ebadi, Pierre-Marie Roy, Olivier Sanchez, Jeannot Schmidt, Maarten van Smeden, Cecile Tromeur, Marije ten Wolde, Marc Righini, Grégoire Le Gal, Menno V. Huisman, Frederikus A. Klok, on behalf of the CT-PE-Pregnancy Group and Artemis Investigators

J Thromb Haemost. 2023 Mar;21(3):606-615

ABSTRACT

Background: Few studies evaluated the performance of non-invasive diagnostic strategies for suspected acute pulmonary embolism (PE) in pregnant women.

Objectives: The aim of this study was to establish the safety and efficiency of the Wells rule with fixed and adapted D-dimer threshold, and the YEARS algorithm, combined with compression ultrasonography (CUS), in pregnant women with suspected PE in an individual patient data meta-analysis.

Methods: We performed a systematic review to identify prospective diagnostic management studies in pregnant patients with suspected PE. Primary outcomes were safety, defined as the failure rate, i.e. the 3-month venous thromboembolism (VTE) incidence after excluding PE without chest imaging, and efficiency, defined as the proportion of patients in whom chest imaging could be avoided.

Results: We identified two relevant studies, of which individual patient-level data were analyzed in a fixed effect meta-analysis, totaling 893 pregnant women. The Wells rule with fixed and adapted D-dimer threshold as well as the YEARS algorithm could safely rule out acute PE (failure rate 0.37-1.4%), but efficiency improved considerably when applying pre-test probability adapted D-dimer thresholds. The efficiency of bilateral CUS was limited (2.3% overall; number needed to test 43), especially in patients without symptoms of deep-vein thrombosis (efficiency 0.79%; number needed to test 127).

Conclusion: This study supports the latest guideline recommendations (European Society of Cardiology 2019) to apply pre-test probability assessment and D-dimer tests to rule out PE in pregnant women. From an efficiency perspective, the use of a strategy with pre-test probability adapted D-dimer threshold is preferred. The yield of CUS was very limited in patients without concomitant symptoms of deep-vein thrombosis.

INTRODUCTION

Pulmonary embolism (PE) is one of the leading causes of maternal death in developed countries, accounting for 15-20% of all deaths.[1-3] The hypercoagulable state in pregnancy, in combination with vascular damage and venous stasis, leads to a 4-5 times higher risk of venous thromboembolism (VTE) in pregnant women, compared to non-pregnant women of the same age.[4,5] At the same time, overlap exists between symptoms of VTE and physiological symptoms of a normal pregnancy and thus PE is often suspected. Moreover, because of the well-known risks of missing a PE diagnosis, the threshold to test for PE during pregnancy is low, which results in a low 4-5% PE prevalence in pregnant women investigated for the disease, compared to a PE prevalence of ~ 12% in same-age non-pregnant women.[6,7]

In the non-pregnant population, recommended diagnostic strategies for suspected PE consist of clinical pre-test probability assessment using validated clinical decision rules (CDRs), D-dimer testing and when indicated, chest imaging. A non-high clinical probability in combination with a normal D-dimer test safely rules out acute PE without imaging.[8-10] The yield of these non-invasive diagnostic strategies has been considerably improved by the introduction of D-dimer thresholds dependent on age or clinical pre-test probability (CPTP).[11-14] Yet, evidence on the safety of these strategies in pregnant patients is limited and D-dimer levels are known to physiologically increase during pregnancy, limiting the ability to exclude PE without imaging.[15] As a consequence, most pregnant patients with suspected PE are referred for imaging, which is complicated by concerns about radiation exposure to both mother and fetus.

International guidelines present contradictory recommendations regarding the use of diagnostic strategies for suspected PE in pregnant women.[16-20] In recent years, two prospective studies evaluating diagnostic strategies in pregnant patients were performed.[21,22] To support harmonization of international guidelines, we set out to evaluate the safety and efficiency of non-invasive diagnostic strategies in pregnant women with suspected PE, by performing a systematic review followed by an individual patient data meta-analysis (IPDMA) of available studies in the setting of pregnancy.

Some of the results of this study have been previously reported in the form of an abstract for the International Society on Thrombosis and Haemostasis (ISTH) Congress of 2020.[23]

METHODS

This IPDMA was pre-registered at the PROSPERO database for systematic reviews (ID CRD42019145414) and followed the guidance of both the PRISMA-IPD and PRISMA-DTA Statement on systematic reviews including individual patient data.[24,25]

Data Sources and Searches

We searched the databases of PubMed, Embase, Web of Science, Cochrane Library, and EMcare until July 1, 2021, to retrieve studies that had evaluated diagnostic strategies for suspected PE in pregnancy. Case reports and reviews were excluded, but no language restrictions were applied. The full search string is provided in the **Appendix**. Two authors (MAMS and TM) independently screened the titles and abstracts of the identified articles and independently assessed the full-text articles for eligibility. Discrepancies were resolved by discussion between the two authors.

Study Selection

Study designs eligible for inclusion were prospective studies that included consecutive pregnant patients with clinically suspected acute PE who were prospectively managed according to a predefined diagnostic strategy, starting with determination of clinical pre-test probability and D-dimer testing. To be eligible, at least 50 pregnant patients per study were required. At the individual level, both outpatients and inpatients were eligible and the minimum duration of follow-up of these patients had to be one month. Patients receiving therapeutic dose anticoagulants initiated 24 hours or more before inclusion in the study were excluded.

Data Extraction and Quality Assessment

Principal investigators from the studies fulfilling the inclusion criteria were asked to provide their deidentified individual patient data (IPD; **Appendix Flowchart**). Before datasets were delivered, variables were recoded by using a specific template developed for this study, to ensure harmonization between studies. This recoding of individual patient data was performed by local personnel who were familiar with the data. A template of the patient-level data that was collected at baseline and follow-up is shown in the **Appendix**. Two authors (MAMS and TM) independently assessed each study from which we retrieved IPD for potential sources of bias, by using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool (**Appendix**).[26] Disagreements were resolved by discussion.

Data Synthesis and Analysis

The main analysis focused on the diagnostic performance of strategies for ruling out suspected PE in the setting of pregnancy. Diagnostic strategies that could be evaluated for the present analysis were the Wells rule and the YEARS algorithm, both combined with D-dimer testing, and if indicated CUS. Despite that one of the included studies applied a diagnostic strategy using the revised Geneva score, this score could not be evaluated in this study, as many patients in this IPD missed Geneva specific items. With regard to the Wells rule and the YEARS algorithm: while the YEARS algorithm is a strategy with D-dimer dependent on CPTP[11], the Wells rule applies 1) a fixed threshold (<500 µg/L), 2) an age-adjusted threshold (age × 10 µg/L in patients aged >50 years or <500 µg/L in patients aged ≤50)[13], or 3) a threshold dependent on CPTP[12]. For the Wells strategy with the fixed D-dimer threshold we used the dichotomized Wells rule, which classifies patients as PE unlikely (Wells score 0-4) or PE likely (≥4.5). For the Wells strategy with the D-dimer threshold dependent on CPTP we used the trichotomized Wells rule, which classifies patients as low (Wells score 0-4), moderate (4.5-6.0) or high (≥6.5) CPTP.[12] The Wells rule with age-adjusted D-dimer threshold was not evaluated as this threshold is irrelevant in this young patient population (all patients were <50 years old). To evaluate the Wells rule and YEARS algorithm in patients that were not primarily managed by these strategies, we reclassified patients to these strategies post-hoc, based on the prospectively collected data from the original study.

The main outcome measures were sensitivity and specificity as well as safety and efficiency of the diagnostic strategies. Sensitivity and specificity were calculated as the number of true positive test results (referral for imaging by the strategy) and true negative test results (PE considered excluded based on the strategy), respectively, with confirmed VTE at baseline or during follow-up as the reference standard. Safety was defined as the failure rate, which is the proportion of patients with confirmed VTE at baseline or during 3-months follow-up divided by the total number of patients in whom PE could be considered excluded at baseline based on a non-high pre-test probability and a negative D-dimer test result, and in whom therapeutic anticoagulant therapy was withheld (as a measure of missed VTE events at baseline). VTE diagnosis had to be confirmed by objective imaging tests, or in the case of death, by autopsy or if no other cause of death could be identified. Traditionally, the generally accepted safety threshold of the point estimate ranges between 2-3%, with recent data suggesting to use a safety threshold dependent on PE prevalence at baseline.[27] The efficiency of the diagnostic strategies was defined as the proportion of patients in whom PE was considered ruled out based on CDR and D-dimer alone, thus in whom chest imaging could be avoided, among all included patients. As CUS was integrated at baseline in the pregnancy adapted diagnostic strategies for suspected PE, the efficiency outcome took into account any positive

CUS for proximal DVT, as chest imaging was deemed unnecessary after a DVT diagnosis. These outcomes were calculated overall and in clinically relevant patient subgroups: first (0-12 weeks) versus second (13-26 weeks) versus third (27-42 weeks) trimester pregnancy, history of VTE, and outpatients versus inpatients.

Secondary outcome measures were the diagnostic performance of CUS (overall and for patients with symptoms of DVT separately), the proportion of non-diagnostic test results and proportion of positive test results (among patients investigated with these tests), the baseline prevalence of acute PE (overall and trimester-specific) and the risk of PE-related death in the studied population. The diagnostic performance of performing CUS of the legs at baseline, in the diagnostic management of suspected PE, was evaluated with confirmed VTE at baseline or during follow-up as the reference standard.

Statistical Analysis

Patient baseline characteristics were described using standard descriptive statistics. Patient level data of the two studies were pooled and analyzed in a fixed effect meta-analysis. Before performing this fixed effect meta-analysis, we excluded study-specific clustering of relevant patient characteristics between the two studies in a multivariable model. Of note, default meta-analytic techniques could not be used in this study after we identified only two potentially relevant studies, because with these techniques the between study-variance cannot be estimated with any precision.

Primary and secondary outcomes were reported as percentages with corresponding exact 95% confidence intervals. SPSS Statistics version 25.0 was used for data analysis.

Role of the Funding source

No funding was received to perform this study.

RESULTS

Study selection and included patients

The literature search retrieved 2,435 studies, of which 47 were assessed for eligibility (**Appendix**). After full-text review 45 studies were excluded, mostly because of an ineligible study design. Consequently, we identified only two studies that fulfilled the pre-defined eligibility criteria.[21,22]

Characteristics and outcomes of the two included studies are summarized in **Appendix Table 1**. Both studies had a prospective study design, included pregnant patients with

clinically suspected PE, and applied a predefined diagnostic strategy starting with assessment of CPTP and D-dimer testing. The CT-PE pregnancy study[21] applied the revised Geneva score, in combination with the fixed D-dimer threshold of 500 µg/L, whereas the Artemis study[22] applied the (pregnancy-adapted) YEARS algorithm, in which 3 items of the original Wells rule are combined with a D-dimer threshold which is dependent on CPTP. CUS of the legs was integrated in both diagnostic study algorithms, although with a different indication, and if CUS was positive for the presence of a proximal DVT, PE diagnosis was considered to be established in both studies. In the CT-PE pregnancy study, bilateral CUS was performed in all patients with a high pretest probability or a positive D-dimer result regardless of the presence or absence of leg symptoms, while in the Artemis study, patients underwent CUS of the symptomatic leg only when symptoms of DVT were present during the initial assessment of pre-test probability by the 3 YEARS items. Baseline prevalence of acute PE, defined as both confirmed PE and proximal DVT at baseline, was 7.1% in the CT-PE study and 4.0% in the Artemis study. In both studies, PE was considered ruled out in patients 1) with negative results on the diagnostic work-up, 2) who did not receive anticoagulant treatment, and 3) who were followed for 3 months with no venous thrombotic events during follow-up. There was no heterogeneity in subgroup definitions between the two studies, as study definitions of comorbidities were comparable.

The combined studies totaled 893 pregnant women (**Table 1**). Mean age of the patients was 31 years (standard deviation (SD) 6), and most patients were in the second or third trimester of pregnancy (42% and 42%, respectively). The majority of the women were outpatients (92%), and active smoking, history of VTE and active malignancy were present in 13%, 6.6%, and 0.1% of the patients, respectively. Baseline prevalence of acute PE was 5.4% in the merged database (first trimester: 13%, second trimester: 4.0%, and third trimester: 3.5%). No patients died within 3-month follow-up.

Main outcomes

The sensitivity, specificity, safety (defined as the failure rate) and efficiency, of the different strategies – overall and across subgroups - is presented in **Table 2**. Overall, sensitivity was high for all strategies under evaluation: the Wells rule with the fixed D-dimer threshold and the YEARS algorithm both yielded a sensitivity of 98% (95%CI 89-100 and 95%CI 88-100, respectively), and the Wells rule with D-dimer threshold dependent on CPTP yielded a sensitivity of 90% (95%CI 78-96). Similarly, overall failure rates were low. The failure rate in patients with non-high pre-test probability and a normal D-dimer test was 0.96% (1/104; 95%CI 0.01-5.8) for the Wells rule with fixed D-dimer threshold, 1.4% (5/365; 95%CI 0.49-3.3) for the Wells rule with D-dimer threshold dependent on CPTP, and 0.37% (1/272; 95%CI 0.01-2.3) for the YEARS algorithm. Specificity was highest when

applying the Wells rule with D-dimer threshold dependent on CPTP (44%; 95%CI 40-47), followed by the YEARS algorithm (32%; 95%CI 29-36), and lowest when applying the Wells rule with the fixed D-dimer threshold (12%; 95%CI 10-15). Equally, the most efficient strategy was the Wells rule with D-dimer threshold dependent on CPTP (43%; 95%CI 40-46), which was followed by the YEARS algorithm (32%; 95%CI 29-35), and least efficient was the strategy applying the Wells rule with the fixed D-dimer threshold (13%; 95%CI 11-15).

Table 1. Baseline characteristics

	CT-PE [21] (N=395)	**Artemis** [22] (N=498)	**Merged** (N=893)
Mean age (+/- SD) – years	31 (6)^	30 (5)^	31 (6)^
Trimester of pregnancy – no (%)			
First: 0 to 12 wk 6 days of gestation	75 (19)	74 (15)	149 (17)
Second: 13 wk 0 days to 26 wk 6 days of gestation	178 (45)	193 (39)	371 (42)
Third: 27 wk 0 days to 42 wk of gestation	142 (36)	231 (46)	373 (42)
YEARS criteria – no (%)			
Patients who met no criteria	91 (24)*	252 (51)	343 (39)*
Patients who met one to three criteria (total no)	284 (76)*	246 (49)	530 (61)*
Clinical symptoms of DVT	59 (15)	47 (9.4)	106 (12)
Hemoptysis	14 (3.5)	19 (3.8)	33 (3.7)
PE as the most likely diagnosis	266 (71)*	218 (44)	484 (55)*
Current smoker – no (%)	71 (18)~	37 (7.8)~	108 (13)~
Previous VTE – no (%)	29 (7.3)	30 (6.0)	59 (6.6)
Active malignancy – no (%)	0 (0)	1 (0.2)	1 (0.1)
Outpatient – no (%)	395 (100)	419 (86)^^	814 (92)^^
Mean heart rate (+/- SD) – bpm	91 (17)**	92 (17)**	92 (17)**
Mean weight (+/- SD) - kg	73 (15)~~	74 (16)~~	74 (16)~~

N/no: number of patients; SD: standard deviation; wk: weeks; DVT: deep-vein thrombosis;
PE: pulmonary embolism; VTE: venous thromboembolism; bpm: beats per minute; kg: kilograms
^This variable was missing in 1 CT-PE and 3 Artemis patients, in total missing in 4 patients
*This variable was missing in 20 CT-PE patients
~This variable was missing in 6 CT-PE and 23 Artemis patients, in total missing in 29 patients
^^This variable was missing in 8 Artemis patients
**This variable was missing in 5 CT-PE and 13 Artemis patients, in total missing in 18 patients
~~This variable was missing in 21 CT-PE and 80 Artemis patients, in total missing in 101 patients

The diagnostic performance of the different strategies varied across different subgroups of patients (**Table 2**). This was particularly the case for the outcome of efficiency. Efficiency was highest in the first trimester of pregnancy, especially when applying a D-dimer threshold dependent on CPTP (64% with the Wells rule and CPTP D-dimer threshold, 54% with the YEARS algorithm, and 35% with the Wells rule and fixed D-dimer threshold). Across all strategies, efficiency was lowest in the third trimester of pregnancy, although efficiency increased considerably when applying an adapted D-dimer threshold. Efficiency was also lower in patients with a history of VTE, versus patients

Table 2. Diagnostic performance of the Wells and YEARS strategy for suspected pulmonary embolism in pregnancy

Pregnancy adapted strategies	Overall	Trimester			Previous VTE		Outpatient	
		First	Second	Third	No	Yes	No	Yes
Wells rule / fixed D-dimer								
Sensitivity (%, 95%CI, n/n)	98 (89-100) 50/51	100 (82-100) 21/21	94 (71-100) 16/17	100 (73-100) 13/13	98 (86-100) 39/40	100 (70-100) 11/11	100 (29-100) 2/2	98 (88-100) 48/49
Specificity (%, 95%CI, n/n)	12 (10-15) 103/835	36 (28-44) 45/126	14 (11-18) 49/352	2.5 (1.3-4.8) 9/357	13 (11-15) 100/787	6.3 (1.5-17) 3/48	10 (4.7-20) 7/69	13 (10-15) 95/759
Failure rate (%, 95%CI, n/n)	0.96 (0.01-5.8) 1/104	0.00 (0.00-9.4) 0/45	2.0 (0.01-11.5) 1/50	0.00 (0.00-34) 0/9	0.99 (0.01-5.9) 1/101	0.00 (0.00-62) 0/3	0.00 (0.00-40) 0/7	1.0 (0.01-6.2) 1/96
Efficiency (number of CTPA scans avoided; %, 95%CI, n/n)*	13 (11-15) 104+11/886	35 (27-43) 45+6/147	14 (11-18) 50+2/369	3.2 (1.8-5.6) 9+3/370	13 (11-16) 101+8/827	10 (4.4-21) 3+3/59	9.9 (4.6-19) 7/71	13 (11-16) 96+11/808
Wells rule / CPTP D-dimer								
Sensitivity (%, 95%CI, n/n)	90 (78-96) 44/49	90 (69-98) 18/20	88 (64-98) 15/17	92 (62-100) 11/12	87 (72-95) 33/38	100 (70-100) 11/11	100 (29-100) 2/2	89 (77-96) 42/47
Specificity (%, 95%CI, n/n)	44 (40-47) 360/821	69 (60-76) 83/121	50 (44-55) 172/347	30 (25-35) 105/353	45 (41-48) 347/775	28 (17-43) 13/46	38 (28-50) 26/68	45 (41-48) 332/746
Failure rate (%, 95%CI, n/n)	1.4 (0.49-3.3) 5/365	2.4 (0.14-8.7) 2/85	1.2 (0.05-4.4) 2/174	0.94 (0.01-5.7) 1/106	1.4 (0.51-3.4) 5/352	0.00 (0.00-27) 0/13	0.00 (0.00-15) 0/26	1.5 (0.53-3.5) 5/337
Efficiency (number of CTPA scans avoided; %, 95%CI, n/n)*	43 (40-46) 365+10/870	64 (56-71) 85+5/141	48 (43-53) 174+2/364	30 (25-35) 106+3/365	44 (41-48) 352+7/813	28 (18-41) 13+3/57	37 (27-49) 26/70	43 (39-46) 337/793

Table 2. Diagnostic performance of the Wells and YEARS strategy for suspected pulmonary embolism in pregnancy (*continued*)

Pregnancy adapted strategies	Overall	Trimester			Previous VTE		Outpatient	
		First	Second	Third	No	Yes	No	Yes
YEARS algorithm								
Sensitivity (%, 95%CI, n/n)	98 (88-100) 47/48	100 (81-100) 20/20	94 (70-100) 15/16	100 (72-100) 12/12	97 (85-100) 36/37	100 (70-100) 11/11	100 (29-100) 2/2	98 (88-100) 45/46
Specificity (%, 95%CI, n/n)	32 (29-36) 270/832	59 (50-67) 73/124	37 (32-42) 129/352	19 (15-24) 68/356	32 (29-36) 255/786	33 (21-47) 15/46	35 (25-47) 24/69	32 (29-36) 245/756
Failure rate (%, 95%CI, n/n)	0.37 (0.01-2.3) 1/271	0.00 (0.00-6.0) 0/73	0.77 (0.01-4.7) 1/130	0.00 (0.00-6.4) 0/68	0.39 (0.01-2.4) 1/256	0.00 (0.00-24) 0/15	0.00 (0.00-16) 0/24	0.40 (0.01-2.5) 1/246
Efficiency (number of CTPA scans avoided; %, 95%CI, n/n)*	32 (29-35) 271+9/880	54 (46-62) 73+5/144	36 (31-41) 130+1/368	19 (16-24) 68+3/368	32 (29-35) 256+6/823	32 (21-45) 15+3/57	34 (24-45) 24/71	32 (29-35) 246+9/802

n: number; CI: confidence interval; CTPA: computed tomographic pulmonary angiography; CPTP: clinical pre-test probability

*As CUS is integrated in the pregnancy adapted diagnostic strategies for suspected PE, the outcome of efficiency takes into account the number of positive compression ultrasonography's (CUS). Thus efficiency is the number of CTPAs avoided based on the strategy plus the number of positive CUS in patients who would have been referred for imaging based on the strategy (as chest imaging is deemed unnecessary after a positive DVT diagnosis).

who did not have a history of VTE. Overall, sensitivity was high for all the strategies under evaluation, in all patient subgroups. Still, summary estimates of the failure rate varied between 0.0-2.4%, with also wide confidence intervals.

The diagnostic performance of CUS of the legs in the management of suspected pulmonary embolism in pregnancy is presented in **Table 3**. Efficiency of CUS - defined as CTPAs avoided because of confirmed proximal DVT - was low, particularly when performing CUS without symptoms of DVT (0.79%; 95%CI 0.16-2.4; number needed to test 127). CUS in women with symptoms of DVT had an efficiency of 7.9% (95%CI 3.9-15; number needed to test 13). Sensitivity of CUS as a stand-alone test for suspected PE was low: 29% (95%CI 17-45) overall, 14% (95%CI 4.1-35) in women without symptoms of DVT, and 47% (95%CI 26-69) in women with symptoms of DVT. Likewise, failure rates of CUS when used as decisive test for suspected PE were high: 5.7% (95%CI 3.9-8.2) overall, 4.8% (95%CI 3.0-7.5) in women without symptoms of DVT, and 9.7% (95%CI 5.0-18) in women with symptoms of DVT. Overall specificity was high, with values of 100%.

Table 3. Diagnostic performance of performing compression ultrasonography of the legs in the diagnostic management of suspected pulmonary embolism in pregnancy

	Sensitivity (%, 95%CI, n/n)	**Specificity** (%, 95%CI, n/n)	**Failure rate **** (%, 95%CI, n/n)	**Efficiency** (number of CTPA scans avoided because confirmed proximal DVT; %, 95%CI, n/n)	**NNT ***** (%, 95%CI, n/n)
CUS * overall	29 (17-45) 11/38	100 (99-100) 444/444	5.7 (3.9-8.2) 27/471	2.3 (1.2-4.1) 11/482	43 (24-83) 100/2.3
CUS * In patients with DVT symptoms	47 (26-69) 8/17	100 (95-100) 84/84	9.7 (5.0-18) 9/93	7.9 (3.9-15) 8/101	13 (7-26) 100/7.9
CUS * In patients without DVT symptoms	14 (4.1-35) 3/21	100 (99-100) 360/360	4.8 (3.0-7.5) 18/378	0.79 (0.16-2.4) 3/381	127 (42-625) 100/0.79

CTPA: computed tomographic pulmonary angiography, NNT: number needed to test, CI: confidence interval, CUS: compression ultrasonography, DVT: deep vein thrombosis

* CUS was performed bilateral in the CT-PE study, while in the Artemis study only the symptomatic leg was tested, both in selected patients (we did not adjust for this difference – all patients with performed CUS were included)

** If used as decisive test

*** NNT to avoid 1 CTPA scan

Chest imaging was performed in patients with a high pre-test probability and/or abnormal D-dimer test result. The frequency of positive test results with CUS, CTPA, and ventilation-perfusion (VQ) scan, and the frequency of non-diagnostic test results with CTPA, is shown in **Appendix Table 2**. The frequency of non-diagnostic test results with

CTPA was overall low (3.8%), yet lower in the Artemis study than in the CT-PE study (0.35% versus 7.0%).

DISCUSSION

The results of this meta-analysis of individual patient data support the use of non-invasive diagnostic strategies in pregnant women with suspected PE, as PE could be ruled out based on a non-high clinical probability and a normal D-dimer test in up to 40% of the patients, thereby reducing the need for chest imaging tests. Importantly, although efficiency in this population of pregnant patients was lower than in the non-pregnant population[8,11,12], efficiency was still considerable and substantially higher when applying a strategy with an adapted D-dimer threshold. Moreover, point estimates of the failure rates were acceptably low and met the proposed criteria for assessing safety of diagnostic strategies for suspected PE (applying a safety threshold dependent on PE prevalence at baseline) in this population of patients with an overall low prevalence of PE.[27-29] In the subgroups, efficiency was lowest, but still clinically relevant, in the third trimester of pregnancy, and although upper limits of the 95% CIs of the failure rates turned out higher due to the relative small sample size in the subgroups, point estimates were acceptably low as well (up to 2.4%).

Until recently, evidence on the best diagnostic approach for suspected PE in pregnant women was lacking. Prior diagnostic studies excluded pregnant patients, mainly because of the unknown safety of these strategies in combination with the presumed futility of D-dimer as a diagnostic test. Two large prospective studies evaluating diagnostic strategies for suspected PE in pregnant patients were recently published: the CT-PE Pregnancy Study[21] and the Artemis Study[22]. These studies were the first to prospectively validate a non-invasive diagnostic strategy for suspected PE in the setting of pregnancy. However, as most guidelines have not been updated with these study results yet, they still present contradictory recommendations regarding the use of non-invasive diagnostic strategies in pregnancy.[16-20] Notably, the pregnancy adapted YEARS algorithm was externally validated in a post-hoc analysis of the CT-PE pregnancy study as well, confirming the greater reduction in chest imaging when applying strategies with an adapted D-dimer threshold, without compromising safety.[30]

In contrast to the application of these strategies in the non-pregnant population, the pregnancy adapted strategies for suspected PE integrate CUS of the legs (performed at baseline) in their strategy, with the goal to avoid chest imaging in patients with confirmed proximal DVT. Importantly, in our study, the efficiency of performing bilateral

CUS was extremely low in patients without symptoms of DVT (0.79%), with a number needed to test (NNT) to avoid 1 CTPA of 127 (which corresponds to having to perform CUS in 254 lower limbs). The efficiency of performing bilateral CUS in patients with symptoms of DVT was higher (7.9%), but still relatively low (NNT 13). Additionally, as is supported by the 3-month incidence of VTE after a negative CUS, it is important not to withhold chest imaging in patients with suspected PE after a negative CUS. These results are in line with previous data.[21] Despite the concerns of radiation exposure in young pregnant women, and the former preference for the VQ scan over CTPA given the lower maternal radiation dose[16,31], more recent studies have now shown that the maternal and fetal risks are similarly low after VQ and modern low radiation dose CTPA, reassuring that both imaging tests can be safely used when indicated.[32-34]

An important strength of our study is that it is the largest study to date to evaluate non-invasive diagnostic strategies for suspected PE in the setting of pregnancy using patient level data of prospective management studies. Whereas a recent meta-analysis did investigate the safety of D-dimer in ruling out VTE in pregnancy, this study did not focus on the performance of clinical probability assessment and D-dimer testing combined on a patient-level basis.[7] In our study we were able to pool the individual patient data of two high quality prospective diagnostic management studies in a fixed effect meta-analysis, which enabled us to analyze almost 900 pregnant patients. Other strengths include the prospective collection of data on clinical probability assessment, the use of a well-accepted diagnostic reference standard, a formal 3-month follow-up with very few lost to follow-up patients, and the homogeneity in subgroup definitions between the two studies.

Limitations of our study need to be discussed as well. First of all, the small number of included studies was a major limitation. This limitation led to a relatively small sample size available for subgroup analyses, resulting in broader 95% confidence intervals of both failure rates and efficiency in these analyses. Second, since the two individual studies evaluated a different diagnostic strategy, a proportion of the patients was not primarily managed by the Wells rule or by the YEARS algorithm as evaluated in this study: the CT-PE pregnancy study has indeed used the revised Geneva score to assess CPTP. Consequently, patients from this study were reclassified according to Wells categories/ YEARS items post-hoc, which could have resulted in information bias. Nevertheless, this reclassification was performed on the basis of prospectively collected data, including the item “PE is the most likely diagnosis”. Unfortunately, we were not able to evaluate the revised Geneva score in this systematic review of individual patient data, as the patients that were enrolled from the Artemis study missed Geneva specific scoring items. Third, although CUS was integrated in both diagnostic study algorithms, CUS was used

at a different stage of the algorithm between the studies, and with a different indication (unselected application of the test versus symptom-driven). Fourth, with regard to the evaluation of non-diagnostic test results, it is important to recall that while the proportion of inconclusive CTPA test results was a predefined endpoint in the CT-PE pregnancy study, in the Artemis study these were only defined as such when a treatment decision could not be made based on the quality of the scan. This presumably explains the difference that was found between the CT-PE and Artemis study in inconclusive CTPA test results. Lastly, the definition of variables included in the diagnostic strategies differed between the two studies, as in some patients the variables were scored based on the Geneva scoring items, and in other patients based on the Wells scoring items.

In conclusion, in our study, the Wells rule combined with D-dimer testing as well as the pregnancy adapted YEARS algorithm safely ruled out acute PE in pregnant patients. Therefore, this study supports the latest guidelines recommendations (ESC 2019[19]) to apply pre-test probability assessment and D-dimer tests to rule out PE in non-high risk pregnant women, thereby reducing the need for chest imaging tests. From an efficiency perspective, we support the use of strategies with pre-test probability adapted D-dimer thresholds. The yield of CUS is very limited, especially in patients without concomitant symptoms of DVT.

REFERENCES

1. Kuriya A, Piedimonte S, Spence AR, Czuzoj-Shulman N, Kezouh A, Abenhaim HA. Incidence and causes of maternal mortality in the USA. J Obstet Gynaecol Res. 2016; 42: 661-8.
2. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006; 367: 1066-74.
3. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance--United States, 1991--1999. MMWR Surveill Summ. 2003; 52: 1-8.
4. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med. 2005; 143: 697-706.
5. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost. 2008; 6: 632-7.
6. Kline JA, Richardson DM, Than MP, Penaloza A, Roy PM. Systematic review and meta-analysis of pregnant patients investigated for suspected pulmonary embolism in the emergency department. Acad Emerg Med. 2014; 21: 949-59.
7. Bellesini M, Robert-Ebadi H, Combescure C, Dedionigi C, Le Gal G, Righini M. D-dimer to rule out venous thromboembolism during pregnancy: A systematic review and meta-analysis. J Thromb Haemost. 2021; 19: 2454-67.
8. van Es N, van der Hulle T, van Es J, et al. Wells Rule and d-Dimer Testing to Rule Out Pulmonary Embolism: A Systematic Review and Individual-Patient Data Meta-analysis. Ann Intern Med. 2016; 165: 253-61.
9. Pasha SM, Klok FA, Snoep JD, et al. Safety of excluding acute pulmonary embolism based on an unlikely clinical probability by the Wells rule and normal D-dimer concentration: a meta-analysis. Thromb Res. 2010; 125: e123-7.
10. Huisman MV, Barco S, Cannegieter SC, et al. Pulmonary embolism. Nat Rev Dis Prim. 2018; 4: 18028.
11. van der Hulle T, Cheung WY, Kooij S, et al. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. Lancet. 2017; 390: 289-97.
12. Kearon C, de Wit K, Parpia S, et al. Diagnosis of Pulmonary Embolism with d-Dimer Adjusted to Clinical Probability. N Engl J Med. 2019; 381: 2125-34.
13. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. Jama. 2014; 311: 1117-24.
14. Robert-Ebadi H, Robin P, Hugli O, et al. Impact of the Age-Adjusted D-Dimer Cutoff to Exclude Pulmonary Embolism. Circulation. 2021; 143: 1828-30.
15. van Mens TE, Scheres LJ, de Jong PG, et al. Imaging for the exclusion of pulmonary embolism in pregnancy. Cochrane Database Syst Rev. 2017; 1: CD011053.
16. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018; 2: 3317-59.
17. Wan T, Skeith L, Karovitch A, Rodger M, Le Gal G. Guidance for the diagnosis of pulmonary embolism during pregnancy: Consensus and controversies. Thromb Res. 2017; 157: 23-8.
18. Royal College of Obstetricians & Gynaecologists. Thromboembolic disease in pregnancy and the puerperium: acute management (green-top guideline No. 37b). 2015.

19. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019; 54.
20. Cohen SL, Feizullayeva C, McCandlish JA, et al. Comparison of international societal guidelines for the diagnosis of suspected pulmonary embolism during pregnancy. Lancet Haematol. 2020; 7: e247-e58.
21. Righini M, Robert-Ebadi H, Elias A, et al. Diagnosis of Pulmonary Embolism During Pregnancy: A Multicenter Prospective Management Outcome Study. Ann Intern Med. 2018; 169: 766-73.
22. van der Pol LM, Tromeur C, Bistervels IM, et al. Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism. N Engl J Med. 2019; 380: 1139-49.
23. Stals M MT, Aujesky D, Bertoletti L, et al. A Non-invasive Diagnostic Work-up Is Safe and Efficient to Exclude Pulmonary Embolism in Low Risk Pregnant Women with Suspected Pulmonary Embolism: A Systematic Review and Meta-analysis [abstract]. Res Pract Thromb Haemost. 2020; 4 (Suppl 1).
24. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. Jama. 2015; 313: 1657-65.
25. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. Jama. 2018; 319: 388-96.
26. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155: 529-36.
27. Dronkers CEA, van der Hulle T, Le Gal G, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. J Thromb Haemost. 2017; 15: 1040-3.
28. Stals MAM, Takada T, Kraaijpoel N, et al. Safety and Efficiency of Diagnostic Strategies for Ruling Out Pulmonary Embolism in Clinically Relevant Patient Subgroups : A Systematic Review and Individual-Patient Data Meta-analysis. Ann Intern Med. 2022; 175: 244-55.
29. Geersing GJ, Takada T, Klok FA, et al. Ruling out pulmonary embolism across different healthcare settings: A systematic review and individual patient data meta-analysis. PLoS Med. 2022; 19: e1003905.
30. Langlois E, Cusson-Dufour C, Moumneh T, et al. Could the YEARS algorithm be used to exclude pulmonary embolism during pregnancy? Data from the CT-PE-pregnancy study. J Thromb Haemost. 2019; 17: 1329-34.
31. Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011; 184: 1200-8.
32. Burton KR, Park AL, Fralick M, Ray JG. Risk of early-onset breast cancer among women exposed to thoracic computed tomography in pregnancy or early postpartum. J Thromb Haemost. 2018; 16: 876-85.
33. Tromeur C, van der Pol LM, Le Roux PY, et al. Computed tomography pulmonary angiography versus ventilation-perfusion lung scanning for diagnosing pulmonary embolism during pregnancy: a systematic review and meta-analysis. Haematologica. 2019; 104: 176-88.
34. Sheen JJ, Haramati LB, Natenzon A, et al. Performance of Low-Dose Perfusion Scintigraphy and CT Pulmonary Angiography for Pulmonary Embolism in Pregnancy. Chest. 2018; 153: 152-60.

APPENDIX: SUPPLEMENTAL MATERIAL

Search string

PubMed

((“diagnosis”[tw] OR “Diagnosis”[Mesh] OR “diagnosis”[Subheading] OR “diagnostic”[tw] OR diagnos*[tw] OR “Tomography, X-Ray Computed”[Mesh] OR “CT”[tw] OR “CAT scan”[tw] OR “CAT scans”[tw] OR “tomography”[tw] OR “tomograph*”[tw] OR “Magnetic Resonance Imaging”[Mesh] OR “magnetic resonance”[tw] OR “MRI”[tw] OR “Ultrasonography”[Mesh] OR “ultrasonography”[tw] OR ultraso*[tw] OR echogra*[tw] OR sonogra*[tw] OR “Angiography”[mesh] OR “angiography”[tw] OR angiogra*[tw] OR “detection”[tw] OR detect*[tw] OR “imaging”[tw] OR “decision rule”[tw] OR “decision rules”[tw] OR “Decision Making”[mesh] OR “Decision Support Techniques”[mesh] OR “Decision Support Systems, Clinical”[Mesh] OR “d-dimer”[tw] OR ddimer*[tw] OR “fibrin fragment D”[Supplementary Concept] OR “Fibrin Fibrinogen Degradation Products”[Mesh] OR “fibrin fragment D1 dimer”[tw] OR “fibrin fragment DD”[tw]) AND (“Pulmonary Embolism”[Mesh] OR “pulmonary embolism”[tw] OR pulmonary embolism*[tw] OR “lung embolism”[tw] OR “lung embolisms”[tw] OR “pulmonary thromboembolism”[tw] OR “pulmonary thromboembolisms”[tw] OR lung thromboembolism[tw] OR “pulmonary thrombo-embolism”[tw] OR “pulmonary embolic”[tw]) AND (“Pregnancy”[Mesh] OR “Pregnancy”[tw] OR “Pregnant”[tw] OR “Pregnant Women”[Mesh] OR Pregnan*[tw] OR “Gestation”[tw] OR “Gravidity”[mesh] OR “Gravidity”[tw] OR “Pregnancy in Adolescence”[mesh] OR “Pregnancy, High-Risk”[mesh] OR “Pregnancy, Multiple”[mesh] OR “Superfetation”[tw] OR “Pregnancy, Unplanned”[mesh] OR “Pregnancy, Unwanted”[mesh] OR “Labor”[tw] OR “Labour”[tw] OR “Cervical Ripening”[tw] OR “Uterine Contraction”[tw] OR “Maternal-Fetal Exchange”[tw] OR “Parity”[tw] OR “Parturition”[tw] OR “Birth”[tw] OR “Childbirth”[tw] OR “Placentation”[tw] OR “Corpus Luteum Maintenance”[tw] OR “Abortion”[tw] OR “Superfetation”[tw] OR “Pseudopregnancy”[tw])) NOT ((“Case Reports”[ptyp] OR “case report”[ti]) NOT (“Review”[ptyp] OR “ review”[ti] OR “Clinical Study”[ptyp] OR “trial”[ti] OR “RCT”[ti]))

Embase

(((“diagnosis”.ti,ab OR exp *”Diagnosis”/ OR “diagnostic”.ti,ab OR diagnos*.ti,ab OR exp *”Computer Assisted Tomography”/ OR “CT”.ti,ab OR “CAT scan”.ti,ab OR “CAT scans”.ti,ab OR “tomography”.ti,ab OR “tomograph*”.ti,ab OR exp *”Nuclear Magnetic Resonance Imaging”/ OR “magnetic resonance”.ti,ab OR “MRI”.ti,ab OR exp *”Ultrasonography”/ OR “ultrasonography”.ti,ab OR ultraso*.ti,ab OR echogra*.ti,ab OR sonogra*.ti,ab OR exp *”Angiography”/ OR “angiography”.ti,ab OR angiogra*.ti,ab OR “detection”.

ti,ab OR detect*.ti,ab OR “imaging”.ti,ab OR “decision rule”.ti,ab OR “decision rules”.ti,ab OR exp *”Decision Making”/ OR exp *”Decision Support System”/ OR “d-dimer”.ti,ab OR ddimer*.ti,ab OR *”D dimer”/ OR “Fibrin Degradation Product”/ OR “fibrin fragment D1 dimer”.ti,ab OR “fibrin fragment DD”.ti,ab) AND (*”Lung Embolism”/ OR “pulmonary embolism”.ti,ab OR pulmonary embolism*.ti,ab OR “lung embolism”.ti,ab OR “lung embolisms”.ti,ab OR “pulmonary thromboembolism”.ti,ab OR “pulmonary thromboembolisms”.ti,ab OR lung thromboembolism.ti,ab OR “pulmonary thrombo-embolism”.ti,ab OR “pulmonary embolic”.ti,ab) AND (exp *”Pregnancy”/ OR “Pregnancy”.ti,ab OR “Pregnant”.ti,ab OR *”Pregnant Woman”/ OR Pregnan*.ti,ab OR “Gestation”.ti,ab OR exp *”Gravidity”/ OR “Gravidity”.ti,ab OR *”Pregnancy in Adolescence”/ OR *”High-Risk Pregnancy”/ OR *”Multiple Pregnancy”/ OR “Superfetation”.ti,ab OR *”Unplanned Pregnancy”/ OR *”Unwanted Pregnancy”/ OR “Labor”.ti,ab OR “Labour”.ti,ab OR “Cervical Ripening”.ti,ab OR “Uterine Contraction”.ti,ab OR “Maternal-Fetal Exchange”.ti,ab OR “Parity”.ti,ab OR “Parturition”.ti,ab OR “Birth”.ti,ab OR “Childbirth”.ti,ab OR “Placentation”.ti,ab OR “Corpus Luteum Maintenance”.ti,ab OR “Abortion”.ti,ab OR “Superfetation”.ti,ab OR “Pseudopregnancy”.ti,ab)) OR (*”Lung Embolism”/di AND (exp *”Pregnancy”/ OR “Pregnancy”.ti,ab OR “Pregnant”.ti,ab OR *”Pregnant Woman”/ OR Pregnan*.ti,ab OR “Gestation”.ti,ab OR exp *”Gravidity”/ OR “Gravidity”.ti,ab OR *”Pregnancy in Adolescence”/ OR *”High-Risk Pregnancy”/ OR *”Multiple Pregnancy”/ OR “Superfetation”.ti,ab OR *”Unplanned Pregnancy”/ OR *”Unwanted Pregnancy”/ OR “Labor”.ti,ab OR “Labour”.ti,ab OR “Cervical Ripening”.ti,ab OR “Uterine Contraction”.ti,ab OR “Maternal-Fetal Exchange”.ti,ab OR “Parity”.ti,ab OR “Parturition”.ti,ab OR “Birth”.ti,ab OR “Childbirth”.ti,ab OR “Placentation”.ti,ab OR “Corpus Luteum Maintenance”.ti,ab OR “Abortion”.ti,ab OR “Superfetation”.ti,ab OR “Pseudopregnancy”.ti,ab))) NOT ((“Case Report”/ OR “case report”.ti) NOT (“Review”/ OR “ review”.ti OR “Clinical Study”/ OR exp “clinical trial”/ OR “trial”.ti OR “RCT”.ti)) NOT (conference review or conference abstract).

Web of Science

((ti=(“diagnosis” OR “Diagnosis” OR “diagnostic” OR diagnos* OR “Computer Assisted Tomography” OR “CT” OR “CAT scan” OR “CAT scans” OR “tomography” OR “tomograph*” OR “Nuclear Magnetic Resonance Imaging” OR “magnetic resonance” OR “MRI” OR “Ultrasonography” OR “ultrasonography” OR ultraso* OR echogra* OR sonogra* OR “Angiography” OR “angiography” OR angiogra* OR “detection” OR detect* OR “imaging” OR “decision rule” OR “decision rules” OR “Decision Making” OR “Decision Support System” OR “d-dimer” OR ddimer* OR “D dimer” OR “Fibrin Degradation Product” OR “fibrin fragment D1 dimer” OR “fibrin fragment DD”) AND ti=(“Lung Embolism” OR “pulmonary embolism” OR pulmonary embolism* OR “lung embolism” OR “lung embolisms” OR “pulmonary thromboembolism” OR “pulmonary thromboembolisms” OR lung thromboembolism OR “pulmonary thrombo-embolism” OR “pulmonary em-

bolic") AND ts=("Pregnancy" OR "Pregnancy" OR "Pregnant" OR "Pregnant Woman" OR Pregnan* OR "Gestation" OR "Gravidity" OR "Gravidity" OR "Pregnancy in Adolescence" OR "High-Risk Pregnancy" OR "Multiple Pregnancy" OR "Superfetation" OR "Unplanned Pregnancy" OR "Unwanted Pregnancy" OR "Labor" OR "Labour" OR "Cervical Ripening" OR "Uterine Contraction" OR "Maternal-Fetal Exchange" OR "Parity" OR "Parturition" OR "Birth" OR "Childbirth" OR "Placentation" OR "Corpus Luteum Maintenance" OR "Abortion" OR "Superfetation" OR "Pseudopregnancy")) OR (ts=("diagnosis" OR "Diagnosis" OR "diagnostic" OR diagnos* OR "Computer Assisted Tomography" OR "CT" OR "CAT scan" OR "CAT scans" OR "tomography" OR "tomograph*" OR "Nuclear Magnetic Resonance Imaging" OR "magnetic resonance" OR "MRI" OR "Ultrasonography" OR "ultrasonography" OR ultraso* OR echogra* OR sonogra* OR "Angiography" OR "angiography" OR angiogra* OR "detection" OR detect* OR "imaging" OR "decision rule" OR "decision rules" OR "Decision Making" OR "Decision Support System" OR "d-dimer" OR ddimer* OR "D dimer" OR "Fibrin Degradation Product" OR "fibrin fragment D1 dimer" OR "fibrin fragment DD") AND ti=("Lung Embolism" OR "pulmonary embolism" OR pulmonary embolism* OR "lung embolism" OR "lung embolisms" OR "pulmonary thromboembolism" OR "pulmonary thromboembolisms" OR lung thromboembolism OR "pulmonary thrombo-embolism" OR "pulmonary embolic") AND ti=("Pregnancy" OR "Pregnancy" OR "Pregnant" OR "Pregnant Woman" OR Pregnan* OR "Gestation" OR "Gravidity" OR "Gravidity" OR "Pregnancy in Adolescence" OR "High-Risk Pregnancy" OR "Multiple Pregnancy" OR "Superfetation" OR "Unplanned Pregnancy" OR "Unwanted Pregnancy" OR "Labor" OR "Labour" OR "Cervical Ripening" OR "Uterine Contraction" OR "Maternal-Fetal Exchange" OR "Parity" OR "Parturition" OR "Birth" OR "Childbirth" OR "Placentation" OR "Corpus Luteum Maintenance" OR "Abortion" OR "Superfetation" OR "Pseudopregnancy"))) NOT ti=(("Case Report" OR "case report") NOT ("Review" OR " review" OR "Clinical Study" OR "clinical trial" OR "trial" OR "RCT"))

Cochrane Library

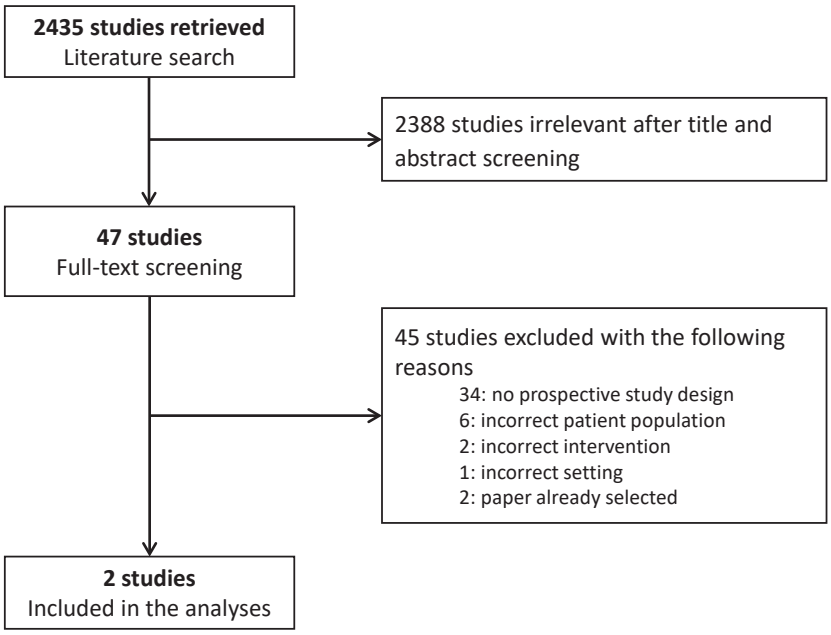
(("diagnosis" OR "Diagnosis" OR "diagnostic" OR diagnos* OR "Computer Assisted Tomography" OR "CT" OR "CAT scan" OR "CAT scans" OR "tomography" OR "tomograph*" OR "Nuclear Magnetic Resonance Imaging" OR "magnetic resonance" OR "MRI" OR "Ultrasonography" OR "ultrasonography" OR ultraso* OR echogra* OR sonogra* OR "Angiography" OR "angiography" OR angiogra* OR "detection" OR detect* OR "imaging" OR "decision rule" OR "decision rules" OR "Decision Making" OR "Decision Support System" OR "d dimer" OR ddimer* OR "D dimer" OR "Fibrin Degradation Product" OR "fibrin fragment D1 dimer" OR "fibrin fragment DD") AND ("Lung Embolism" OR "pulmonary embolism" OR pulmonary embolism* OR "lung embolism" OR "lung embolisms" OR "pulmonary thromboembolism" OR "pulmonary thromboembolisms" OR lung thromboembolism OR "pulmonary thrombo embolism" OR "pulmonary embolic") AND

(“Pregnancy” OR “Pregnancy” OR “Pregnant” OR “Pregnant Woman” OR Pregnan* OR “Gestation” OR “Gravidity” OR “Gravidity” OR “Pregnancy in Adolescence” OR “High Risk Pregnancy” OR “Multiple Pregnancy” OR “Superfetation” OR “Unplanned Pregnancy” OR “Unwanted Pregnancy” OR “Labor” OR “Labour” OR “Cervical Ripening” OR “Uterine Contraction” OR “Maternal Fetal Exchange” OR “Parity” OR “Parturition” OR “Birth” OR “Childbirth” OR “Placentation” OR “Corpus Luteum Maintenance” OR “Abortion” OR “Superfetation” OR “Pseudopregnancy”)):ti,ab,kw

Emcare

((“diagnosis”.ti,ab OR exp *”Diagnosis”/ OR “diagnostic”.ti,ab OR diagnos*.ti,ab OR exp *”Computer Assisted Tomography”/ OR “CT”.ti,ab OR “CAT scan”.ti,ab OR “CAT scans”.ti,ab OR “tomography”.ti,ab OR “tomograph*”.ti,ab OR exp *”Nuclear Magnetic Resonance Imaging”/ OR “magnetic resonance”.ti,ab OR “MRI”.ti,ab OR exp *”Ultrasonography”/ OR “ultrasonography”.ti,ab OR ultraso*.ti,ab OR echogra*.ti,ab OR sonogra*.ti,ab OR exp *”Angiography”/ OR “angiography”.ti,ab OR angiogra*.ti,ab OR “detection”.ti,ab OR detect*.ti,ab OR “imaging”.ti,ab OR “decision rule”.ti,ab OR “decision rules”.ti,ab OR exp *”Decision Making”/ OR exp *”Decision Support System”/ OR “d-dimer”.ti,ab OR ddimer*.ti,ab OR *”D dimer”/ OR “Fibrin Degradation Product”/ OR “fibrin fragment D1 dimer”.ti,ab OR “fibrin fragment DD”.ti,ab) AND (*”Lung Embolism”/ OR “pulmonary embolism”.ti,ab OR pulmonary embolism*.ti,ab OR “lung embolism”.ti,ab OR “lung embolisms”.ti,ab OR “pulmonary thromboembolism”.ti,ab OR “pulmonary thromboembolisms”.ti,ab OR lung thromboembolism.ti,ab OR “pulmonary thrombo-embolism”.ti,ab OR “pulmonary embolic”.ti,ab) AND (exp *”Pregnancy”/ OR “Pregnancy”.ti,ab OR “Pregnant”.ti,ab OR *”Pregnant Woman”/ OR Pregnan*.ti,ab OR “Gestation”.ti,ab OR exp *”Gravidity”/ OR “Gravidity”.ti,ab OR *”Pregnancy in Adolescence”/ OR *”High-Risk Pregnancy”/ OR *”Multiple Pregnancy”/ OR “Superfetation”.ti,ab OR *”Unplanned Pregnancy”/ OR *”Unwanted Pregnancy”/ OR “Labor”.ti,ab OR “Labour”.ti,ab OR “Cervical Ripening”.ti,ab OR “Uterine Contraction”.ti,ab OR “Maternal-Fetal Exchange”.ti,ab OR “Parity”.ti,ab OR “Parturition”.ti,ab OR “Birth”.ti,ab OR “Childbirth”.ti,ab OR “Placentation”.ti,ab OR “Corpus Luteum Maintenance”.ti,ab OR “Abortion”.ti,ab OR “Superfetation”.ti,ab OR “Pseudopregnancy”.ti,ab)) NOT ((“Case Report”/ OR “case report”.ti) NOT (“Review”/ OR “ review”.ti OR “Clinical Study”/ OR exp “clinical trial”/ OR “trial”.ti OR “RCT”.ti))

Flowchart of included studies



Template Patient-level Data

See Appendix A Online

Appendix Table 1. Characteristics of included studies

Study; Year (ref)	Diagnostic strategy	Study period	D-dimer assay	Diagnostic imaging test	Outcome adjudication	Number of patients ; N	Patients with VTE at baseline or during FU; N (%)
Righini et al, 2018 [21]	Assessment of pre-test probability by applying the revised Geneva score, in combination with D-dimer testing (fixed D-dimer threshold of 500 µg/L). PE was considered to be ruled out in patients with low or intermediate clinical probability and a negative D-dimer result. All other patients first underwent bilateral CUS. If DVT was confirmed, PE was considered to be present. If negative, chest imaging was subsequently performed.	August 2008 – July 2016	VIDAS	CTPA (or alternatively VQ)	Yes	395	28 (7.1%)
Van der Pol et al, 2019 [22]	Assessment of pre-test probability by applying the YEARS algorithm with D-dimer testing (D-dimer threshold dependent on CPTP: 1000 µg/L in patients with low CPTP and 500 µg/L in patients with high CPTP). Patients with symptoms of DVT (first YEARS item) underwent CUS of the symptomatic leg. If DVT was confirmed, chest imaging was not performed anymore, and PE was considered to be present. In patient with no YEARS items and a D-dimer <1000 µg/L, and in patients with 1-3 YEARS items and a D-dimer <500 µg/L, PE was considered to be ruled out. All patients in whom PE had not been ruled out underwent chest imaging.	October 2013 – May 2018	VIDAS, Tina-quant, STA-Liatest, Innovance, HemosIL	CTPA (or alternatively VQ)	Yes	498	21 (4.2%)

Bias risk assessment using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool

QUADAS-2 summary of results							
Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
CT-PE Pregnancy Study (2018)	☺	☺	☺	☺	☺	☺	☺
Artemis Study (2019)	☺	☺	☺	☺	☺	☺	☺

☺ = low risk of bias, low level of applicability concerns

Appendix Table 2. Test characteristics in the management of suspected pulmonary embolism in pregnancy

	Proportion of positive test results* (%, n/n)	Proportion of non-diagnostic test results^ (%, n/n)
CUS		
CT-PE	1.9% 7/361	NA
Artemis	3.3% 4/122	NA
Merged	2.3% 11/483	NA
CTPA		
CT-PE	5.5% 19/344	7.0% 24/344
Artemis	5.2% 15/287	0.35% 1/287
Merged	5.4% 34/631	3.8% 24/631
VQ		
CT-PE	14% 4/29	NA
Artemis	50% 1/2	NA
Merged	16% 5/31	NA

n: number; CUS: compression ultrasonography; CTPA: computed tomographic pulmonary angiography; VQ: ventilation-perfusion scan

* Proportion of positive test results among patients investigated with this test at baseline (for CUS, CTPA and VQ separately)

^ Proportion of non-diagnostic test results among patients investigated with this test at baseline (information only available for CTPA)