ORIGINAL ARTICLE

Pregnancy-Adapted YEARS Algorithm for Diagnosis of Suspected Pulmonary Embolism

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ABSTRACT

BACKGROUND

Pulmonary embolism is one of the leading causes of maternal death in the Western world. Because of the low specificity and sensitivity of the D-dimer test, all pregnant women with suspected pulmonary embolism undergo computed tomographic (CT) pulmonary angiography or ventilation–perfusion scanning, both of which involve radiation exposure to the mother and fetus. Whether a pregnancy-adapted algorithm could be used to safely avoid diagnostic imaging in pregnant women with suspected pulmonary embolism is unknown.

METHODS

In a prospective study involving pregnant women with suspected pulmonary embolism, we assessed three criteria from the YEARS algorithm (clinical signs of deep-vein thrombosis, hemoptysis, and pulmonary embolism as the most likely diagnosis) and measured the D-dimer level. Pulmonary embolism was ruled out if none of the three criteria were met and the D-dimer level was less than 1000 ng per milliliter or if one or more of the three criteria were met and the D-dimer level was less than 500 ng per milliliter. Adaptation of the YEARS algorithm for pregnant women involved compression ultrasonography for women with symptoms of deep-vein thrombosis; if the results were positive (i.e., a clot was present), CT pulmonary angiography was not performed. All patients in whom pulmonary embolism had not been ruled out underwent CT pulmonary angiography. The primary outcome was the incidence of venous thromboembolism at 3 months. The secondary outcome was the proportion of patients in whom CT pulmonary angiography was not indicated to safely rule out pulmonary embolism.

RESULTS

A total of 510 women were screened, of whom 12 (2.4%) were excluded. Pulmonary embolism was diagnosed in 20 patients (4.0%) at baseline. During follow-up, popliteal deep-vein thrombosis was diagnosed in 1 patient (0.21%; 95% confidence interval [CI], 0.04 to 1.2); no patient had pulmonary embolism. CT pulmonary angiography was not indicated, and thus was avoided, in 195 patients (39%; 95% CI, 35 to 44). The efficiency of the algorithm was highest during the first trimester of pregnancy and lowest during the third trimester; CT pulmonary angiography was avoided in 65% of patients who began the study in the first trimester and in 32% who began the study in the third trimester.

CONCLUSIONS

Pulmonary embolism was safely ruled out by the pregnancy-adapted YEARS diagnostic algorithm across all trimesters of pregnancy. CT pulmonary angiography was avoided in 32 to 65% of patients. (Funded by Leiden University Medical Center and 17 other participating hospitals; Artemis Netherlands Trial Register number, NL5726.)

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*A complete list of the Artemis Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Acute pulmonary embolism is one of the leading causes of maternal death in Western countries; the overall incidence is reported to be 1.72 cases per 1000 deliveries, and it accounts for approximately one death in every 100,000 deliveries.[1-4] A wide overlap exists between the clinical symptoms of venous thromboembolism (VTE) and symptoms caused by physiological changes in pregnancy, such as tachycardia, swelling of the legs, and dyspnea. However, because of the well-known elevated risk of VTE with potentially fatal pulmonary embolism during pregnancy, the threshold to test for pulmonary embolism during pregnancy is low. This clinical dilemma is best indicated by published reports that show a prevalence of pulmonary embolism of 5% or less among pregnant women in whom pulmonary embolism is suspected, as compared with a rate of 15 to 20% among nonpregnant women.[5,6]

Studies that have validated the use of clinical decision rules or D-dimer tests to rule out pulmonary embolism without the use of imaging tests during pregnancy are scarce,[7] and recent publications have called into question the safety of such practices.[8,9] A recent study showed that pulmonary embolism could be ruled out without computed tomographic (CT) pulmonary angiography in only 16% of pregnant women on the basis of a decision rule, D-dimer test, and compression ultrasonography of both legs.[9] Therefore, the diagnostic workup of pregnant women with suspected pulmonary embolism relies mainly on imaging of the chest (i.e., CT pulmonary angiography or ventilation–perfusion scanning), with associated potential harm to the mother and fetus through exposure to intravenous contrast enhancement and ionizing radiation.[10-12] Because of the lack of strong evidence for validated diagnostic algorithms, there is no consensus among international guidelines regarding the approach to take in the diagnosis of pulmonary embolism during pregnancy.[12-14]

Recently, the YEARS study (Netherlands Trial Register number, NL4020) assessed the use of the diagnostic YEARS algorithm in men and women with clinically suspected pulmonary embolism. The study showed that the algorithm had a low incidence of failure, as evidenced by the incidence of VTE at 3 months of 0.61% (95% confidence interval [CI], 0.39 to 0.96), and that the use of CT pulmonary angiography was 14 percentage points lower when the YEARS algorithm was applied than when conventional algorithms were applied. These findings were observed in all age groups and across several relevant subgroups.[15] We conducted a prospective study to evaluate the use of a pregnancy-adapted YEARS algorithm in the management of suspected pulmonary embolism in pregnant women (Fig. 1).

METHODS

STUDY DESIGN AND OVERSIGHT

The Artemis study was a multicenter, international study that was conducted at 11 academic and 7 nonacademic teaching hospitals. From October 2013 through May 2018, we consecutively screened pregnant women who were 18 years of age or older and had been referred to the emergency department or the obstetrical ward because of suspected pulmonary embolism, which was defined by new onset or worsening of chest pain or dyspnea, with or without hemoptysis or tachycardia. Exclusion criteria were treatment with a full-dose therapeutic anticoagulant agent that had been initiated 24 hours or more before the eligibility assessment, unavailability of the patient for follow-up, allergy to iodinated contrast enhancement, or a life expectancy of 3 months or less. In the YEARS study, which was initiated in 2013, pregnancy was not an exclusion criterion. However, very few pregnant women participated in the study, and we decided to continue the study in pregnant women only. This extension study and its protocol, available with the full text of this article at NEJM.org, were approved by the institutional review board at the Leiden University Medical Center (for all participating hospitals in the Netherlands) and by the institutional review board at the Brest University Hospital Center, Brest (for all participating hospitals in France). The institutional review board in Leiden waived the need for informed consent from study participants at the hospitals in the Netherlands and the institutional review board in Brest waived the need for informed consent from study participants at the hospitals in France, a decision that was endorsed by the local institutional review board at each participating site. In Ireland, the institutional review board at the

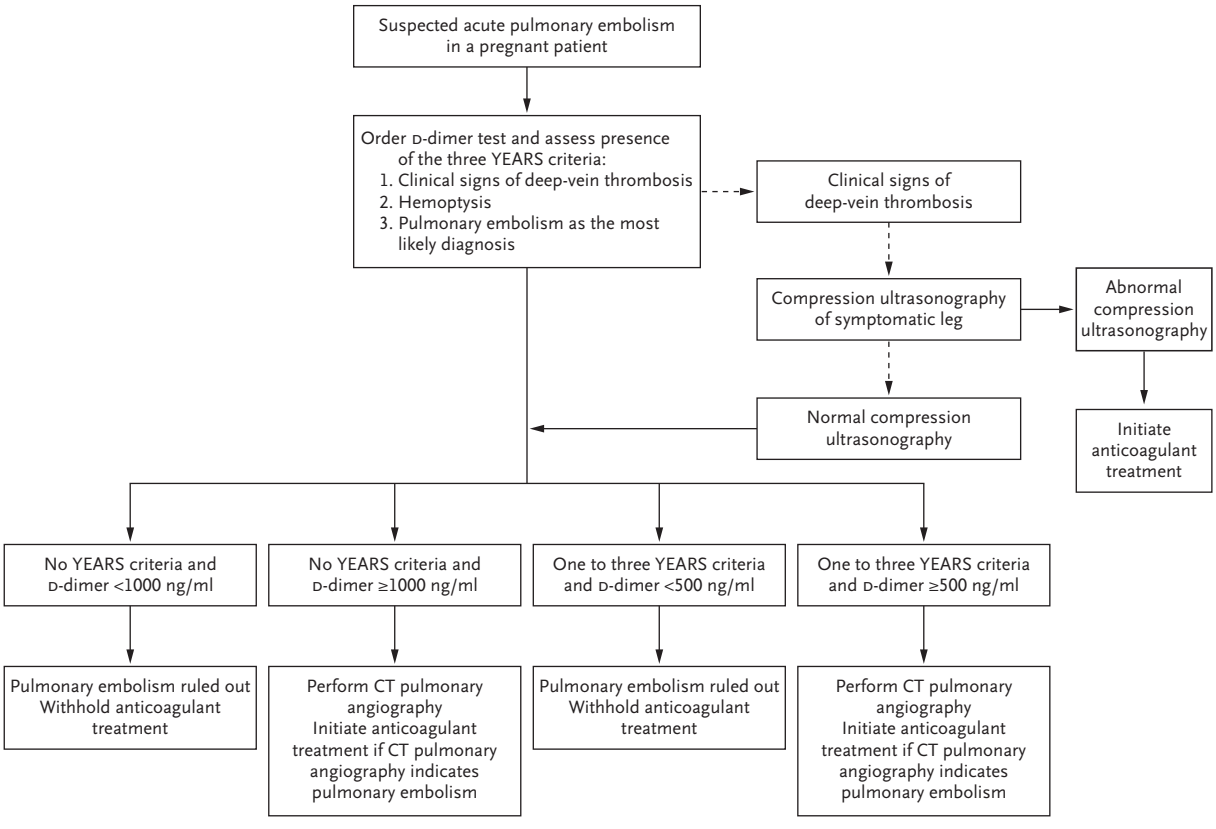

Figure 1. Pregnancy-Adapted YEARS Algorithm for the Management of Suspected Acute Pulmonary Embolism in Pregnant Patients.
CT denotes computed tomography.

Rotunda Hospital approved the study protocol, and the patients at the site provided written informed consent. The study was designed by the authors with no involvement of any commercial entity. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the study to the protocol. No one who is not an author contributed to the writing of the manuscript.

PROCEDURES

The attending physician evaluated whether a clinical suspicion of pulmonary embolism was present on the basis of the patient's reported symptoms, including sudden onset of dyspnea or chest pain. If pulmonary embolism was suspected, management followed the prespecified pregnancy-adapted YEARS algorithm (Fig. 1). Three criteria from the YEARS algorithm were assessed in all the patients: whether clinical signs of deep-vein thrombosis were present, whether hemoptysis (which was defined as the coughing up of small amounts of blood or a streak of blood) was reported, and whether pulmonary embolism was considered by the physician to be the most likely diagnosis. The third criterion (pulmonary embolism as the most likely diagnosis, above any alternative diagnosis) was evaluated on the basis of the patient's history and physical examination results, as was originally proposed by Wells et al.[16] These three criteria were chosen because they had been shown to be the most predictive for pulmonary embolism in an earlier post hoc analysis that was performed to construct the YEARS algorithm.[17] The D-dimer level, which was assessed in parallel with the confirmation of suspicion of pulmonary embolism and the assessment of the YEARS criteria, was measured with the use of automated, well-validated, high-sensitivity, quantitative D-dimer assays (VIDAS

D-Dimer Exclusion, bioMérieux; Tina-quant, Roche Diagnostica; STA-Liatest, Diagnostica Stago; Innovance, Siemens; or HemosIL, Instrumentation Laboratory). Because of the strict parallel timing of the assessment of YEARS criteria and the measurement of the D-dimer level, physicians may occasionally have been aware of the D-dimer result when they were assessing the YEARS criteria.

Patients who had clinical signs of deep-vein thrombosis underwent two-point compression ultrasonography of the deep veins of the symptomatic leg (at the popliteal and inguinal levels) to confirm or rule out proximal deep-vein thrombosis. In the case of confirmed deep-vein thrombosis, a diagnosis of pulmonary embolism was considered to be established, and no other diagnostic imaging test was performed. In the case of either absence of signs of deep-vein thrombosis or a normal compression ultrasonogram, the rest of the algorithm was followed. If a patient did not meet any of the three YEARS criteria and the D-dimer level was less than 1000 ng per milliliter or if a patient met one or more of the three YEARS criteria and the D-dimer level was less than 500 ng per milliliter, a diagnosis of pulmonary embolism was considered to be ruled out, and anticoagulant treatment was withheld. All the remaining patients were referred for CT pulmonary angiography, which was considered to be the diagnostic standard, to confirm or rule out the diagnosis of acute pulmonary embolism.

Before the start of the study, local procedures for CT pulmonary angiography were adapted and standardized for pregnancy (e.g., a high flow rate of administration of contrast medium, a high concentration of contrast medium, a shallow breath hold [to avoid the Valsalva maneuver], and a reduced dose of radiation).[10] Patients in whom the diagnosis of pulmonary embolism was ruled out were followed for 3 months for the occurrence of symptomatic VTE.

Patients were instructed to return to the hospital before the 3-month appointment if symptoms of VTE occurred, at which time objective tests to diagnose or rule out the disease were performed. Patients who had confirmed pulmonary embolism, deep-vein thrombosis, or both were treated with therapeutic low-molecular-weight heparin in accordance with international guidelines.[13]

OUTCOMES

The primary outcome was the cumulative incidence of symptomatic VTE, with confirmation by objective tests, during a 3-month follow-up period in the subgroup of patients in whom anticoagulant treatment was withheld on the basis of a negative result of the algorithm (i.e., a diagnosis of pulmonary embolism was ruled out). Pulmonary embolism was considered to be present if CT pulmonary angiography with contrast enhancement showed a new filling defect in a subsegmental or more proximal pulmonary artery.[18] A death was classified as having been caused by pulmonary embolism if the presence of a pulmonary embolism was confirmed on autopsy or was shown by objective testing before death or if sudden death occurred for which no other cause could be identified. Proximal deep-vein thrombosis was considered to be present if compression ultrasonography showed noncompressibility of a proximal vein (i.e., the popliteal vein or a more proximal vein).[18] An independent committee assessed and adjudicated all suspected cases of VTE and deaths that occurred during follow-up.

The secondary outcome was the proportion of patients in whom CT pulmonary angiography was not indicated to safely rule out pulmonary embolism. The results of this analysis were compared with those of a hypothetical situation in which all the patients would have undergone CT pulmonary angiography or ventilation–perfusion scanning.[12-14]

STATISTICAL ANALYSIS

Assuming a 1.0% incidence of recurrence of symptomatic VTE during the 3-month follow-up period and considering a maximum incidence of recurrence of 2.7% as the upper limit of a safe strategy, we estimated that a sample of 425 patients who did not have pulmonary embolism according to the algorithm and who completed follow-up would provide 80% power to reject the null hypothesis that the incidence of recurrence of symptomatic VTE would be greater than 2.7%, at an overall one-sided alpha level of 0.05, using a binominal test.[19] Assuming a 5% prevalence of pulmonary embolism at baseline, we determined that a total of 445 pregnant women with suspected pulmonary embolism should be included. Finally, anticipating a 5%

incidence of loss to follow-up, we aimed to include 469 patients.

For the analysis of the primary outcome, which assessed the safety of the algorithm, we used a per-protocol approach. For the analysis of the secondary outcome, which assessed the efficiency of the algorithm, we used both an intention-to-diagnose approach and a per-protocol approach.[15] The difference between the two approaches was the way in which we reported the proportion of patients in whom CT pulmonary angiography was performed but not indicated by the algorithm. Cases in which pulmonary embolism was diagnosed at presentation on the basis of CT pulmonary angiography that was not indicated were considered to be a failure of the diagnostic strategy. Prespecified subgroup analyses were planned to assess the pregnancy-adapted YEARS algorithm during each of the three trimesters. An analysis of the worst-case scenario was performed in which all patients who were lost to follow-up were considered to have had a diagnosis of VTE during follow-up. The primary and secondary outcomes are reported as percentages with corresponding exact 95% confidence intervals. Analyses were performed with the use of SPSS software, version 23.0.

RESULTS

PATIENTS

A total of 510 consecutive pregnant women with clinically suspected pulmonary embolism were screened at the 18 participating hospitals; 12 of the women (2.4%) were excluded for various reasons (Fig. 2). The baseline characteristics of the 498 patients who participated in the study are summarized in Table 1. The highest percentage of patients enrolled in the study were in the third trimester of pregnancy (46%). A total of 30 patients (6.0%) had previously had VTE, and 14 patients (2.8%) had known thrombophilia.

Among the 498 patients, 252 (51%) did not meet any of the three YEARS criteria, and 246 (49%) met at least one of the YEARS criteria. Of the latter 246 patients, hemoptysis was present in 19 (7.7%), clinical signs of deep-vein thrombosis were present in 47 (19%), and pulmonary embolism was considered to be the most likely diagnosis in 218 (89%).

Of the 47 patients who had clinical signs of deep-vein thrombosis, 43 underwent compression ultrasonography, which confirmed deep-vein thrombosis in 3 (7%). A total of 79 patients underwent compression ultrasonography of the legs in the absence of clinical signs of deep-vein thrombosis, of whom 1 patient (1%) received a diagnosis of deep-vein thrombosis. This patient met one YEARS criterion (pulmonary embolism was considered to be the most likely diagnosis) and had a D-dimer level of 1480 ng per milliliter. Proximal deep-vein thrombosis was thus confirmed in a total of 4 patients (Fig. 2).

The D-dimer level was below the prespecified threshold in 195 of the 494 patients (39%) who did not have confirmed deep-vein thrombosis. Of the 299 patients who had a D-dimer level that was higher than the relevant threshold, 2 patients in whom CT pulmonary angiography was indicated were referred for ventilation–perfusion scanning, 273 patients underwent CT pulmonary angiography, and 24 patients did not undergo CT pulmonary angiography (which constituted a protocol violation). Acute pulmonary embolism was confirmed in 16 patients on the basis of CT pulmonary angiography (15 patients) or ventilation–perfusion scanning (1 patient). Of the 16 patients, 1 did not meet any of the YEARS criteria (0.4% of the 252 patients who met no YEARS criteria) but had a D-dimer level above the prespecified threshold, and 15 met at least one of the YEARS criteria (6.2% of the 242 patients who met at least one criterion) and had a D-dimer level above the threshold; none of the 16 patients had deep-vein thrombosis (Fig. 2). The total number of patients who had pulmonary embolism at baseline was therefore 20 (4.0%; 95% CI, 2.6 to 6.1); this total included the 4 patients in whom proximal deep-vein thrombosis was confirmed by compression ultrasonography. No adverse reactions occurred as a result of CT pulmonary angiography.

One patient (0.20%) who did not meet any of the YEARS criteria at presentation and who had a D-dimer level of 980 ng per milliliter was temporarily lost to follow-up. Subsequent follow-up revealed that she had not had symptomatic VTE before giving birth without incident 2 months later.

OUTCOMES

Among the 477 patients (96%) in whom pulmonary embolism was ruled out at baseline, who

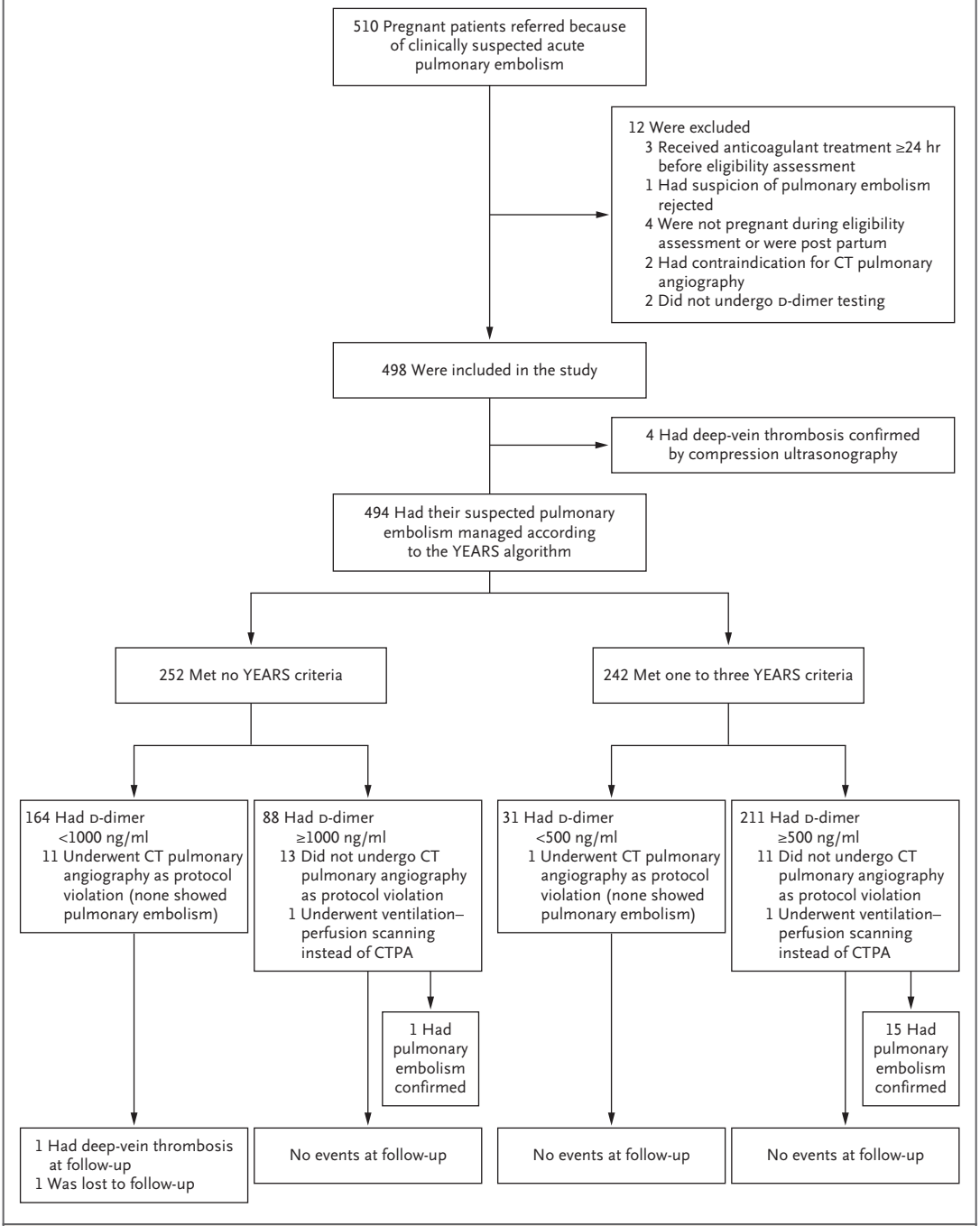

Figure 2. Enrollment of Patients and Diagnostic Workup at Baseline and during Follow-up.

remained untreated during follow-up, and who completed the follow-up period, 1 patient received a diagnosis of VTE during follow-up (0.21%; 95% CI, 0.04 to 1.2) (Table 2). This patient, who had not met any YEARS criteria and had had a D-dimer level of 480 ng per milliliter and therefore had not undergone CT pulmonary angiography, received a diagnosis of symptomatic pop-

liteal deep-vein thrombosis, which was confirmed by compression ultrasonography on day 90 of the follow-up period. No patient received a diagnosis of pulmonary embolism during the follow-up period. In an analysis of the worst-case scenario, which assumed that all patients who were lost to follow-up would have had a diagnosis of VTE during the 3-month follow-up period, the incidence of VTE at 3 months among patients who did not undergo CT pulmonary angiography would have been 0.42% (2 of 478 patients; 95% CI, 0.11 to 1.5).

Among the 195 patients who should not have undergone CT pulmonary angiography (because they did not have confirmed deep-vein thrombosis and had a D-dimer level below the prespecified threshold), 12 patients (6.2%) underwent CT pulmonary angiography, which constituted a protocol violation; no evidence of pulmonary embolism was observed in any of the 12 patients. When the intention-to-diagnose approach was used, CT pulmonary angiography was not performed in 195 of the 494 patients in whom deep-vein thrombosis was not diagnosed at baseline (39%; 95% CI, 35 to 44); the per-protocol approach yielded similar results (40% [183 of 459 patients]; 95% CI, 35 to 45).

The results of the analyses performed in the subgroups of patients defined according to the trimester of pregnancy during which the patient was enrolled in the study are summarized in Table 3. Pulmonary embolism was diagnosed at presentation in 5 of 74 patients (6.8%; 95% CI, 2.9 to 15) in the first trimester, in 8 of 193 patients (4.2%; 95% CI, 2.1 to 8.0) in the second trimester, and in 7 of 231 patients (3.0%; 95% CI, 1.5 to 6.1) in the third trimester. The median D-dimer level was 505 ng per milliliter (interquartile range, 292 to 963) during the first trimester, 730 ng per milliliter (interquartile range, 505 to 1260) during the second trimester, and 1120 ng per milliliter (interquartile range, 818 to 1718) during the third trimester. The safety of the algorithm to rule out pulmonary embolism was similar among the three trimesters. The efficiency of the algorithm was highest during the first trimester and lowest during the third trimester; CT pulmonary angiography was avoided in 65% of the patients who began the study in the first trimester and in 32% of the patients who began the study in the third trimester.

Table 1. Demographic and Baseline Characteristics of Pregnant Patients with Suspected Pulmonary Embolism.*

Characteristic	Patients (N=498)
Mean age (±SD) — yr	30±5.8
Median duration of pregnancy (IQR) — wk	25 (17–31)
Trimester of pregnancy — no. (%)	
First: 0 to 12 wk 6 days of gestation	74 (15)
Second: 13 wk 0 days to 26 wk 6 days of gestation	193 (39)
Third: 27 wk 0 days to 42 wk of gestation	231 (46)
YEARS criteria — no. (%)	
Patients who met no criteria	252 (51)
Patients who met one to three criteria	246 (49)
Clinical signs of deep-vein thrombosis	47 (19)
Hemoptysis	19 (7.7)
Pulmonary embolism as the most likely diagnosis	218 (89)
First pregnancy — no. (%)	133 (27)
Median duration of reported symptoms (IQR) — days	2 (1–6)
Air travel in the previous 4 wk — no. (%)	12 (2.4)
Surgery in the previous 4 wk — no. (%)	5 (1.0)
Immobilization for >3 days in the previous 4 wk — no. (%)	31 (6.2)
Current smoker — no. (%)	37 (7.4)
Known asthma — no. (%)	62 (12)
Previous VTE — no. (%)	30 (6.0)
Known thrombophilia — no. (%)	14 (2.8)
Outpatient — no. (%)	419 (84)

* IQR denotes interquartile range, and VTE venous thromboembolism.

DISCUSSION

Our study showed that the pregnancy-adapted YEARS algorithm was able to safely rule out pulmonary embolism in pregnant women with suspected pulmonary embolism. CT pulmonary angiography was avoided in 39% of the patients, thus averting potential harm from radiation exposure.[12,13] Avoidance of CT pulmonary angiography occurred in 65% of patients during the first trimester (when radiation is potentially most harmful to the fetus), 46% of patients during the second trimester, and 32% of patients during the third trimester. This decreasing specificity can be explained by the physiological rise in the D-dimer level that commonly occurs during pregnancy.[7] At the time of presentation, a 4.0% incidence of pulmonary embolism was observed, whereas the

Table 2. Primary and Secondary Outcomes.*

Variable	All Patients (N=498)	Patients Who Did Not Have Deep-Vein Thrombosis at Baseline (N=494)	
		CT Pulmonary Angiography Not Indicated	CT Pulmonary Angiography Indicated†
Pulmonary embolism confirmed at baseline			
No./total no.	20/498‡	0/195	16/299
% (95% CI)	4.0 (2.6–6.1)	0 (0.0–2.0)	5.4 (3.3–8.5)
Diagnosis of VTE during follow-up in patients who did not have VTE at baseline			
No./total no.	1/477§	1/195	0/283
% (95% CI)	0.21 (0.04–1.2)¶	0.51 (0.09–2.9)‖	0 (0.00–1.4)

* CT denotes computed tomography.
† Ventilation–perfusion scanning was performed instead of CT pulmonary angiography in 2 patients.
‡ Four of the 498 patients had deep-vein thrombosis, which was confirmed by compression ultrasonography.
§ The denominator of 477 comprises all patients who did not have VTE at baseline and who were not lost to follow up.
¶ These results represent the primary outcome.
‖ These results represent the secondary outcome.

Table 3. Study Outcomes, According to Trimester of Pregnancy.

Variable	First Trimester (N=74)	Second Trimester (N=193)	Third Trimester (N=231)
Pulmonary embolism confirmed at baseline			
No./total no.	5/74	8/193	7/231
% (95% CI)	6.8 (2.9–15)	4.2 (2.1–8.0)	3.0 (1.5–6.1)
CT pulmonary angiography not indicated*			
No./total no.	48/74	89/193	74/231
% (95% CI)	65 (54–75)	46 (39–53)	32 (26–38)
Diagnosis of VTE during follow-up†			
No./total no.	0	1/176	0
% (95% CI)		0.57 (0.1–3.2)	
Median D-dimer level (IQR) — ng/ml	505 (292–963)	730 (505–1260)	1120 (818–1718)

* Results are from an intention-to-diagnose analysis.
† Results are from a per-protocol analysis.

incidence was 5.4% among patients referred for CT pulmonary angiography. This low incidence was expected and was consistent with the 2% incidence observed in a retrospective study that evaluated an algorithm that was based on ventilation–perfusion scanning.[20] The 3-month incidence of symptomatic VTE in the current study was low, with only one patient (0.21%) receiving a diagnosis of proximal deep-vein thrombosis and no patient receiving a diagnosis of pulmonary embolism during follow-up. These data meet the proposed criteria for assessing the safety of diagnostic methods in VTE, even in the context of a low baseline prevalence of disease.[19]

Our algorithm provides solid evidence for the safe management of suspected pulmonary embolism in pregnant women, with selective use of CT pulmonary angiography. In another study, an algorithm that involved pretest assessment of clinical probability with the use of the revised

Geneva score, high-sensitivity D-dimer testing, compression ultrasonography of both legs in all patients irrespective of symptoms, and CT pulmonary angiography showed that pulmonary embolism was diagnosed in 7.1% of 395 pregnant women at initial presentation and in no women at follow-up.[9] However, CT pulmonary angiography — or ventilation–perfusion scanning in a minority of cases — was indicated in 84% of patients in that study, as compared with only 61% in the current study, and the low 1.7% diagnostic yield of abnormal compression ultrasonography was associated with the costly approach of performing ultrasonography of both legs in all patients.[9] In a recent study, the risk of early breast cancer was found to be similarly low after ventilation–perfusion scanning and CT pulmonary angiography, which supports the notion that both imaging methods are valid options in patients without cardiopulmonary disease.[21]

Some issues warrant comment. First, the pregnancy-adapted YEARS algorithm was applied only in patients in whom a clear suspicion of pulmonary embolism was raised, and it was not used as a primary screening test for pulmonary embolism in pregnant women who had nonspecific chest symptoms. Second, both the pregnancy-adapted YEARS algorithm and the YEARS algorithm are driven largely by the criterion that assessed whether pulmonary embolism was considered to be the most likely diagnosis. However, the other two YEARS criteria were present in a relevant percentage of patients (19% had clinical signs of deep-vein thrombosis and 7.7% had hemoptysis). The subjective criterion that assessed whether pulmonary embolism was the most likely diagnosis is also the most decisive variable of the Wells score, which has been recommended as an initial diagnostic test for suspected pulmonary embolism in the nonpregnant population for more than a decade.[22] Third, in our study, the D-dimer level could have occasionally been known to the physician when the YEARS criteria were determined, a circumstance that could potentially have led to either attributing less importance to the criterion of pulmonary embolism as the most likely diagnosis when the result of the D-dimer test was low or attributing more importance to that criterion when the D-dimer result was high. However, when the Wells clinical decision rule is used in clinical practice, the D-dimer level is also often available before the total sum of the Wells rule is calculated.[23,24] In the YEARS and Artemis studies, close to 4000 patients with suspected pulmonary embolism had the diagnostic process managed according to a standardized algorithm in daily clinical practice conditions, often by junior physicians, in academic and teaching hospitals and across several European countries; these studies provided reassuring external validity of the YEARS approach. This measure of external validity, together with the positive results of the current study (i.e., the very low number of diagnostic failures and high efficiency of the algorithm), strongly supports the relevance and generalizability of the pregnancy-adapted YEARS approach and the YEARS approach.[15] Finally, the safety of applying a D-dimer threshold on the basis of pretest probability of pulmonary embolism has been shown in other international studies.[25,26] In addition, the YEARS algorithm has been shown to be associated with a reduction in the detection of potentially clinically irrelevant subsegmental pulmonary embolism and with both a shorter visit time and reduced costs in the emergency department.[27,28]

Strengths of our study include the prospective design, large sample size, and near complete follow-up. Limitations are the nonrandomized design and the occurrence of protocol violations. However, the very low observed incidence of failure at 3 months and the near complete follow-up and the use of a standard design for evaluating diagnostic algorithms of VTE strongly support the chosen design.[15,29-32] The protocol violations reflect the great challenge of managing suspected pulmonary embolism in pregnant women, which is largely fueled by concerns of both the physician and the patient regarding radiation exposure, as well as the lack of solid evidence to guide the diagnostic strategy. Indeed, the most prevalent risk factor for improper diagnostic management of suspected pulmonary embolism has been reported to be pregnancy.[33] The protocol violations did not lead to unwanted outcomes in our study population, nor did they affect our primary or secondary outcome.

In conclusion, the pregnancy-adapted YEARS diagnostic algorithm safely ruled out acute pulmonary embolism in pregnant patients who were

referred for suspected pulmonary embolism. The main advantage of this approach was that CT pulmonary angiography was averted in 32 to 65% of the patients, depending on the trimester of presentation, without compromising safety.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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