Pregnancy as a predictor of deviations from the recommended diagnostic pathway in women with suspected pulmonary embolism: ZATPOL registry data

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Abstract

Introduction: Pulmonary embolism (PE) is a leading cause of mortality in pregnancy and a great diagnostic challenge. Deviations from the recommended diagnostic pathway in suspected PE contribute to greater mortality in the general population. The deviations from the guidelines of the European Society of Cardiology (ESC) for diagnosis of PE were analyzed, with particular emphasis on pregnant women with suspected PE.

Material and methods: ZATPOL is a prospective national registry including data of all patients with suspected PE admitted to 86 Polish cardiology departments between January 2007 and September 2008. We analyzed diagnostic pathways used in all 2015 patients (mean age: 67 ±15 years, 60% women) with suspected PE. Detailed analysis included diagnostic pathways used in 12 pregnant patients and 85 non-pregnant women in childbearing age.

Results: Pregnancy was the strongest predictor of deviations from the recommended diagnostic pathway in the whole study group (HR = 4.0, 95% CI: 1.28–12.5, p = 0.02). Pregnant patients did not differ significantly from non-pregnant women in most risk factors and symptoms of PE, and diagnostic tests used in this condition. Deviations from the recommended diagnostic pathway were found in 7 (58%) and 36 (42%) pregnant and non-pregnant women, respectively (p = 0.297), and the preliminary diagnosis of PE was eventually confirmed in 42% and 67% of the patients, respectively (p = 0.086).

Conclusions: Despite the lack of significant differences in PE symptomatology in pregnant and non-pregnant women, pregnancy seems to be the strongest predictor of deviations from the diagnostic pathway recommended in PE by the ESC. Further studies are required to evaluate the adherence to current guidelines in pregnant women.

Key words: pulmonary embolism, pregnancy, diagnosis, registry.

Introduction

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality in both the general population and pregnant women from developed countries [1]. The diagnostic pathway in pulmonary embolism (PE) starts with doctors' suspicion of this condition. Although PE is one of the most common cardiovascular conditions, it does not produce any characteristic symptom that would expedite the differential diagnosis. Despite an increase in clinical experience and a growing body of published evidence, including the European Society of Cardiology (ESC) guidelines, diagnosis of VTE is still highly challenging, in particular in pregnancy. This is primarily related to non-specific symptoms and signs of this condition, especially in pregnant patients [2].

The most typical symptoms that may raise a suspicion of PE are dyspnea, chest pain, pre-syncope or syncope, and/or hemoptysis [1]. However, pleuritic chest pain and hemoptysis seem to be the only symptoms that are more frequent in patients with established PE than in individuals in whom this condition has been eventually ruled out [3]. In the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) study, the most common manifestation of PE was dyspnea, present in 73% of the subjects, followed by pleuritic chest pain, cough, calf or thigh swelling and non-pleuritic chest pain [4].

In some cases, imaging tests that require exposure to ionizing radiation need to be conducted to confirm/rule out PE, and some physicians may be reluctant to perform such tests in pregnant women. As a result, diagnostic pathways used in pregnant women with suspected PE may frequently differ from those used in non-pregnant patients.

The aim of this study was to identify predictors of deviations from the recommended diagnostic pathway in PE. Specifically, we verified whether diagnostic pathways used to confirm/rule out PE in pregnant patients were different from those used in non-pregnant women. Moreover, we analyzed the most common deviations from the ESC-recommended diagnostic pathway that occurred during evaluation of pregnant women with suspected PE.

Material and methods

ZATPOL (acronym derived from the Polish name: Rejestr ZATorowości Płucnej w POLsce) is a prospective registry including data of all patients with suspected PE, who were diagnosed at 86 Polish cardiology departments in 2006–2008. Suspected PE was defined as presence of clinical symptoms suggesting PE, such as dyspnea, cough, hemoptysis, chest pain, collapse or suggesting deep vein thrombosis. In 41% of patients elevated D-dimer levels and in 6% signs of pulmonary hypertension in echocardiography were reported as symptoms suggesting PE. In 5.1% of patients in the ZATPOL registry PE was diagnosed after discovering thrombi in pulmonary vessels in computed tomography performed due to other reasons.

The idea of the registry and its detailed organization have been presented elsewhere [5, 6]. Briefly, ZATPOL was established to verify whether the diagnostic pathways used to confirm/rule out PE in Polish patients are consistent with the respective guidelines published by the European Society of Cardiology. Physicians who dealt with subjects with suspected PE provided detailed data of their patients via an internet-based platform. Before they were included in the registry, correctness and completeness of the data were verified by authorized specialists. Recorded data included patients' demographics, hospitalization details, signs and symptoms present on admission, comorbidities, history of previous anticoagulation treatment, risk factors for VTE, clinical classification of PE severity, clinical probability of PE, details of diagnostic process and results of additional tests, such as chest X-ray, electrocardiogram, arterial blood gas test, echocardiogram, as well as D-dimer concentration, venous ultrasound (VUS), computed tomography angiography (angio-CT), inpatient and outpatient treatment and outcome.

In the Polish centers participating in the ZATPOL Registry in the years 2007–2008 chest angio-CT was available round-the-clock in 44% of centers. In 20% of centers patients could undergo chest angio-CT during daily working hours, in 16% this test could be done only in another hospital. Ten percent of centers reported lack of possibility to perform chest angio-CT up to 7 days. For 10% of patients the data were missing.

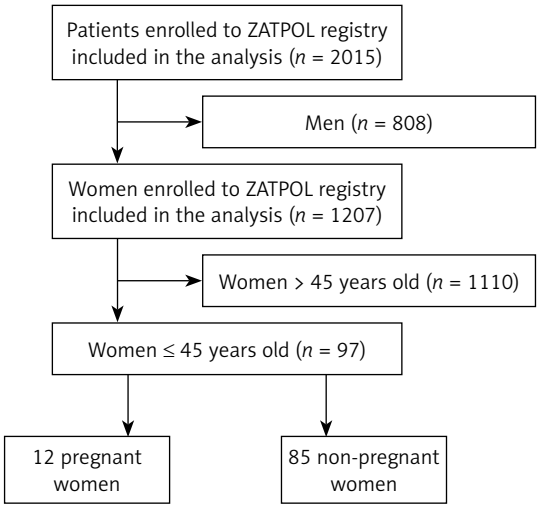

Figure 1. Flow chart illustrating selection of patients from ZATPOL registry

Predictors of deviations from the diagnostic pathway recommended in PE were analyzed for the whole set of patients included in the ZATPOL registry (n = 2015), and separately for 12 pregnant patients and 85 non-pregnant women in childbearing age (18–45 years). Details of the selection process are presented in Figure 1.

Statistical analysis

Predictors of deviations from the recommended diagnostic pathway were identified in univariate logistic regression analysis. The results for the group of pregnant patients were analyzed separately and then compared with the results for non-pregnant women of childbearing age. Since the series included only 12 pregnant women, the analysis was restricted solely to descriptive statistics. Normal distribution of the study variables was verified with the Shapiro-Wilk test. Statistical characteristics of normally distributed continuous variables are presented as means ± standard deviations (SD), and the characteristics of variables with distributions other than normal are shown as medians and interquartile ranges (IQR). Distributions of categorical variables are presented as numbers and percentages. Owing to the small number of pregnant women in our series, the Mann-Whitey U-test was used for intergroup comparisons. Distributions of categorical variables within the study groups were compared with the χ^2 test. All statistical calculations were carried out with the SPSS 21 package, with the threshold of statistical significance set at $p < 0.05$.

Results

Characteristics of study subjects

Data of 2015 patients, 1207 (60%) women and 808 (40%) men, with mean age of 67 ±15 years, were included in the ZATPOL registry. While non-high risk PE was suspected in the vast majority of the subjects (n = 1710, 85%), a subset of patients (n = 305, 15%) presented with shock or hypotension at the beginning of the diagnostic process. One thousand one hundred and ten out of 1207 women included in the registry were older than 45 years. The group of women aged 45 years or less included 12 patients who were pregnant at the time of evaluation. Characteristics of these subjects were compared to those of non-pregnant women of corresponding age.

Comparative analysis included signs and symptoms presented at the time of evaluation, as well as characteristics of the diagnostic process. Detailed characteristics of pregnant and non-pregnant women are presented in Table I. The two groups did not differ in terms of age (30.0 ±3.7 vs. 31.5 ±7.9, p = 0.113), prevalence of PE symptoms (Table II) or concomitant cardiovascular diseases. Two established risk factors of PE, obesity (33% vs. 0%, p = 0.018) and oral contraceptive use (44% vs. 8%, p = 0.019), were significantly more often found in non-pregnant women than in pregnant patients.

Pregnancy as a predictor of deviations from the diagnostic pathway recommended in PE

We verified which of the parameters (medical history data, clinical findings and results of additional tests) included in the ZATPOL registry were significant predictors of deviations from the recommended diagnostic pathway in the whole cohort of 2015 patients. Pregnancy at the time of evaluation was found to be associated with the highest likelihood of deviations from the diagnostic pathway recommended in PE (HR = 4.0, 95% CI: 1.28–12.5, p = 0.02). Other predictors are listed in Table III.

Deviations from the recommended diagnostic pathway in 18- to 45-year-old women

Since pregnancy was identified as the strongest predictor of deviations from the recommended di-

Table I. Comparison of demographic parameters and vital signs of pregnant and non-pregnant women

Parameter	Pregnant (n = 12)	Non-pregnant (n = 85)	P-value
Age [years]	30.0 ±3.7	31.5 ±7.9	0.113
HR [beats/min]	85.7 ±16.6	98.7 ±18.5	0.058
SBP [mm Hg]	114.8 ±7.1	118.2 ±22.7	0.483
DBP [mm Hg]	72.0 ±12.1	74.5 ±15.1	0.592
Respiratory rate [breaths/min]	18.2 ±3.6	20.3 ±5.8	0.368
Oxygen saturation (%)	95.0 ±3.8	91.7 ±6.8	0.106
Weight [kg]	73.3 ±15.7	72.4 ±18.5	0.570

DBP – diastolic blood pressure, HR – heart rate, SBP – systolic blood pressure. Data are presented as means ± standard deviations.

Table II. Comparison of symptoms present in pregnant and non-pregnant women

Parameter	Pregnancy *n* (%)	Non-pregnancy *n* (%)	*P*-value
Dyspnea upon exercise	8/12 (66.7)	58/85 (68.2)	0.913
Dyspnea at rest	9/12 (75)	46/85 (54.1)	0.172
Pleural chest pain	2/12 (16.7)	25/85 (29.4)	0.356
Angina chest pain	0/12 (0)	10/85 (11.8)	0.210
Indefinite chest pain	4/12 (33.3)	19/85 (22.4)	0.402
Hemoptysis	0/12 (0)	8/85 (9.4)	0.267
Fever	3/12 (25)	19/85 (22.4)	0.838
Fainting	1/12 (8)	27/85 (31.8)	0.094
Palpitations	5/12 (41.6)	48/85 (56.5)	0.335
Hypotony	0/12 (0)	12/85 (14.1)	0.164
Cough	2/12 (16.7)	24/85 (28.2)	0.397
Symptoms of DVT	3/12 (25)	26/85 (30.6)	0.692

DVT – deep vein thrombosis.

Table III. Predictors of deviations from the recommended diagnostic pathway in pulmonary embolism documented in ZATPOL Registry (2015 patients)

Risk factor	Odds ratio	95% confidence interval	*P*-value
Pregnancy	4.00	1.28–12.5	0.02
Systolic blood pressure	1.04	1.07–1.08	0.02
Unspecified type of chest pain	1.25	1.00–1.59	0.004
Obesity	1.26	1.01–1.58	0.04
High-risk PE	1.36	1.02–1.81	0.04
Pleural fluid on chest X-ray	1.37	1.04–1.81	0.03
Varicose vein on lower extremities	1.38	1.10–1.72	0.004
Female sex	1.40	1.10–1.79	0.006
Aspirin intake	1.40	1.12–1.75	< 0.001
Age > 75 years	1.41	1.13–1.77	0.002
Right axis deviation in ECG	1.49	1.07–2.07	< 0.001
Long-term anticoagulation therapy with vitamin K antagonists	1.52	1.05–2.20	0.001
Low clinical probability of PE	1.53	1.16–2.03	0.003
Dyspnea upon rest	1.54	1.20–1.97	< 0.001
History of myocardial infarction treated conservatively	1.64	1.07–2.53	0.02
Pulmonary congestion on chest X-ray	1.67	1.31–2.15	< 0.001
Cardiac enlargement on chest X-ray	1.75	1.41–2.18	< 0.001
Treatment with pressor amines	1.77	1.25–2.52	0.001
Acidosis	1.83	1.27–2.63	< 0.001
Renal insufficiency (eGFR > 30 ml/min)	1.85	1.41–2.43	< 0.001
Pulmonary disease with respiratory insufficiency	1.87	1.26–2.76	0.002
Hypercapnia	1.95	1.32–2.86	< 0.001
Heart failure NYHA III–IV	2.07	1.62–2.64	< 0.001
Hospitalization at a regional hospital	2.18	1.74–2.73	< 0.001
Renal insufficiency (eGFR < 30 ml/min)	2.21	1.23–3.98	0.008

eGFR – estimated glomerular filtration rate, NYHA – New York Heart Association, PE – pulmonary embolism.

agnostic pathway, we verified whether pregnant patients and non-pregnant women of childbearing age (≤ 45 years) were evaluated according to the ESC-recommended protocol.

Deviations from the recommended diagnostic pathway were found in 7 (58%) and 36 (42%) pregnant and non-pregnant women, respectively (p = 0.297). Detailed analysis demonstrated that determination of D-dimer concentration was the only diagnostic test used to confirm/rule out PE in 3 out of 12 pregnant patients and in only 1 out of 85 non-pregnant women. None of these patients were evaluated further despite clinical evidence of suspected PE and elevated D-dimer concentration. The most common diagnostic error made in non-pregnant women (n = 29, 83%) was not performing angio-CT in subjects with high clinical probability PE or in hemodynamically unstable patients. In most patients from this subset, determination of D-dimer concentration was the first diagnostic test. All pregnant women were hemodynamically stable and none of them had high clinical probability of PE.

In 2 pregnant women, detection of elevated D-dimer concentrations was followed by VUS, but no lung tests were conducted despite the lack of ultrasonographic abnormalities. In one pregnant patient with moderate clinical probability of PE and no evidence of hemodynamic instability, chest angio-CT was conducted as the first diagnostic test. In another pregnant woman with elevated D-dimer concentration, angio-CT was performed as the second test instead of VUS.

Less frequent errors made during evaluation of non-pregnant women are described below. Two deviations from the recommended diagnostic pathway were identified in one patient from this subset. First, despite clinical evidence of hemodynamic instability, determination of D-dimer concentration was the first diagnostic test performed in this patient. Second, angio-CT was conducted as the second test although the patient presented with a normal D-dimer level. Another two women were subjected to imaging tests, ventilation perfusion lung scan and angio-CT, although they had low or moderate clinical probability of PE and presented with normal D-dimer levels. D-dimer concentrations were in turn not determined at all in another two women with moderate clinical probability of PE. Finally, no additional tests were conducted in a woman with low clinical probability of PE despite an inconclusive result of ventilation perfusion scan.

Importantly, our series included one non-pregnant woman with moderate clinical probability of PE, whose diagnostic process was continued despite a normal D-dimer level. Owing to the positive result of VUS, this patient was qualified for angio-CT and eventually diagnosed with PE and deep vein thrombosis (DVT). This illustrates that a small fraction of patients with DVT may present with normal D-dimer concentrations, particularly when a lower sensitivity D-dimer test is used.

Comparison of diagnostic process in pregnant and non-pregnant women

Determination of D-dimer concentration was most commonly considered as the first line diagnostic test in both pregnant and non-pregnant women. However, chest angio-CT was conducted as the first test in 11% of non-pregnant patients. Angio-CT was typically performed as the second test (40%), along with VUS (26%) and lung scintigraphy (11%). The ultimate diagnosis of PE was eventually established in 57 out of 85 non-pregnant women (67%) and in 5 out of 12 pregnant patients (42%) (p = 0.086), and DVT was detected in 29/85 (34%) and 3/12 (25%) non-pregnant and pregnant subjects, respectively (p = 0.529). Detailed information about the tests used to establish the final diagnosis in pregnant and non-pregnant women is given in Table IV. While no mortality was documented among pregnant women with suspected PE during a 30-day follow-up, 4 non-pregnant women died during this period.

Discussion

Analysis of the ESC recommendations

The problem of diagnosing PE in pregnant women was first addressed by the ESC in 2008 [7], and the respective guidelines have evolved since then. Nevertheless, authors of all published guide-

Table IV. Comparison of diagnostic tests used to confirm/rule out pulmonary embolism in pregnant and non-pregnant women

Parameter	D-dimer concentration		Chest angio-CT		Venous ultrasound		Lung scintigraphy	
	Pregnant group	Non-pregnant group	Pregnant group	Non-pregnant group	Pregnant group	Non-pregnant group	Pregnant group	Non-pregnant group
% of patients who underwent test	100	89	50	73	66.7	53	0	16
P-value	0.59		0.08		0.54		0.21	

lines emphasize that clinical presentation of PE in pregnant women is the same as in the general population, with the same key clinical symptoms and signs, such as dyspnea, chest pain, tachycardia, hemoptysis and collapse. However, some objective signs, e.g. tachycardia, may be of lesser clinical significance owing to the physiological increase in heart rate in response to pregnancy-related hypervolemia [8]. Furthermore, some symptoms that may suggest PE are also commonly reported by women in physiological pregnancies; for example, more than 75% of pregnant women in the third trimester complain of dyspnea [9].

What makes the lack of specific symptoms even more troubling is the immense magnitude of the diagnostic issue. In 2007, chest pain with related ailments and shortness of breath were the second and the eighth principal reasons for emergency department visits among 15- to 64-year-old women in the United States [10]. Even more importantly, no significant differences were found in the occurrence of these PE-related symptoms between pregnant and non-pregnant women. Furthermore, problems related to pregnancy and puerperium were identified as the fifth most common reason for referrals to the emergency department [10]. Hypercoagulability observed in pregnancy is a consequence of complex changes in plasma concentrations of clotting and anticlotting factors, e.g. free protein S [11].

Tools allowing adequate prognosis of pregnant patients with PE are another issue demanding further research. There are several means dedicated to risk stratification in the general population, including well-established ones such as troponin and NT-proBNP levels and those yet to be widely used, such as tricuspid annular plane systolic excursion [12]. The validity of scoring systems assessing probability of VTE solely on the basis of clinical presentation has not been verified in pregnant women thus far. Furthermore, women in physiological pregnancies frequently present with elevated D-dimer concentrations [1, 2, 7, 13]. However, according to the 2008 ESC guidelines and more recently published recommendations, normal D-dimer concentration has similar value in excluding PE in pregnant women as in patients from the general population [1, 7]. Therefore, in line with the 2008 ESC guidelines, determination of D-dimer concentration should be the first test conducted in pregnant women with suspected PE [7]. However, according to more recent guidelines published by the same organization in 2014, although the negative predictive value of this parameter has been validated in a number of studies, the usefulness of D-dimer concentration in pregnancy is still a matter of concern. Some experts even recommended using higher cut-off values for D-dimer concentration in pregnant women [1], but to the best of our knowledge, this approach has still not been verified empirically. Nevertheless, all patients with elevated D-dimer concentrations should be subjected to additional diagnostic tests when PE is suspected [1].

In pregnant patients the second step in confirming/excluding PE is bilateral compression ultrasonography (CUS) [1]. If this test reveals presence of thromboembolic material, anticoagulation treatment should be implemented promptly without further testing. However, if no abnormalities are found during CUS, radiological examination of the chest, either CT pulmonary angiography or lung scintigraphy, needs to be performed. Importantly, the diagnostic pathway described above is suitable only for hemodynamically stable patients.

The 2011 ESC guidelines on the management of cardiovascular diseases in pregnant women include a separate section dedicated to venous thromboembolism during pregnancy and puerperium [13]. In line with these guidelines, VTE can be excluded in pregnant women who present with normal D-dimer concentrations and show no abnormalities on CUS; neither anticoagulation therapy nor further diagnostics are required in such cases. However, further evaluation is recommended in patients who present with elevated D-dimer concentrations without concomitant abnormalities on CUS. In such cases, magnetic resonance imaging is the test of choice to exclude iliac vein thrombosis. Whenever this test yields a negative result, pulmonary angio-CT is preferred over ventilation-perfusion lung scanning [13]. However, in the ESC 2014 guidelines, a ventilation-perfusion scan is preferred due to safety concerns [1]. Furthermore, the authors of the guidelines put great emphasis on thorough assessment of VTE risk profile, in terms of both general and pregnancy-specific risk factors [13]. In line with the 2011 guidelines, VTE risk should be assessed in all women in early pregnancy, as well as in those planning to get pregnant. Based on the result, each woman should be assigned to one out of three VTE risk categories and appropriate preventive measures need to be implemented [13, 14].

The most recent ESC guidelines, published in 2014, include several recommendations regarding diagnosis of PE in pregnancy [1]. However, most of them are low-class (IIb) recommendations based on C evidence level, already included in previous editions. According to the authors of the 2014 guidelines, lung scintigraphy in the form of perfusion scanning may be preferred over angio-CT in patients with no abnormalities on chest radiograms, owing to the slightly elevated risk of breast cancer inherent to CT [1]. Ventilation-perfusion scanning is unnecessary. However, angio-CT

should be considered in case of any abnormalities on chest radiograms, or whenever lung scintigraphy is not available and PE cannot be ruled out otherwise (e.g. based on D-dimer concentration or CUS) [1]. Analyzing data from the ZATPOL registry, we did not find significant differences in diagnostic tests used to confirm/rule out PE in pregnant and non-pregnant women.

There is no clear advantage of any of the available lung imaging methods used in diagnosing PE during pregnancy. Both methods expose the fetus to radiation, although below the threshold for potential teratogenesis established at 50 mSv. However, the exposure to the maternal breast tissue during chest angio-CT is estimated to be in the range 10–70 mSv [1]. Exposure to radiation is thought to increase lifelong risk of breast and lung cancer in exposed women [14]. It needs to be underlined that PE is a life-threatening disease and therefore one should not hesitate to use all recommended diagnostic methods including those with ionizing radiation [1].

In pregnant women negative angio-CT and normal ventilation-perfusion scintigraphy are equally reliable in PE exclusion [15]. Both methods are at risk of inconclusive results, but among pregnant patients this probability is higher for angio-CT. However, in pregnant women with abnormal chest X-ray, the rate of nondiagnostic ventilation-perfusion scans is significantly higher [14, 16]. There are two ongoing trials aimed at clarifying unsolved issues of the diagnostic pathway in pregnant women [17]. Therefore the best choice for lung the imaging method during PE diagnosis remains unsolved. It depends on the clinical state of the patient, chest X-ray results and availability of ventilation perfusion scan or angio-CT.

A recent meta-analysis showed that in an emergency department setting, VTE is less often confirmed in pregnant women than in non-pregnant patients [17]. This implies that currently used risk scoring systems and diagnostic algorithms are not necessarily suitable for detection of VTE in pregnant women. Although pregnancy predisposes to thromboembolism, available evidence suggests that VTE is eventually ruled out in most pregnant women who present with signs and symptoms suggestive of this condition. Our findings presented here are consistent with these data, as an ultimate diagnosis of PE was eventually established in 67% and 42% of non-pregnant and pregnant women, respectively.

First, despite the 1-year and 9-month period during which the ZATPOL Registry was carried out, the group of pregnant women in the analyzed data was small. However, it needs to be underlined that the ZATPOL Registry includes data from all over Poland obtained in a prospective fashion, ensuring the high standard of the performed analysis. Second, the ZATPOL Registry was conducted in 2007–2008, almost 10 years ago. Moreover, the adherence to past recommendations was evaluated in this study. However, in those 10 years, despite growing evidence, there have been no substantial changes in the recommendations and guidelines for diagnosing PE. These changes were elaborated carefully and compared between consecutive recommendations in the discussion section of the article. Third, during the analyzed period the availability of diagnostic methods in Poland increased, which might have an influence on the correctness of the diagnostic pathway. It needs to be remembered that in pregnant patients the D-dimer level can be elevated during physiological pregnancy. In our cohort all pregnant patients were hemodynamically stable and therefore our observations do not apply to hemodynamically unstable pregnant patients with PE.

In conclusion, despite the lack of significant differences in PE symptomatology between pregnant and non-pregnant women, pregnancy seems to be the strongest predictor of deviations from the diagnostic pathway recommended in PE by the European Society of Cardiology. Physicians who deal with pregnant patients seem to be particularly prone to deviations from the recommended diagnostic protocol. In some cases, this may result from fetal safety concerns related to radiation exposure, commonly expressed by patients and their families. Interestingly, however, venous compression ultrasonography was not used in all cases included in the series presented here. Even more importantly, the lung perfusion scan was also evidently underutilized in our patients. This is quite surprising, as this test may rule out PE without unnecessary radiation exposure of the breasts, which are particularly vulnerable in pregnant women. That said, it should also be pointed out that the current guidelines regarding diagnosis of PE in pregnancy are not based on robust validated evidence and as such should be considered primarily as expert advice. As the present study was based on a registry carried out almost ten years ago and evaluates deviations from a diagnostic pathway that had been recommended at that time, further studies are required to evaluate the adherence to current guidelines in pregnant women.

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