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EVIDENCE-BASED DIAGNOSTICS

Systematic Review and Meta-analysis of Pregnant Patients Investigated for Suspected Pulmonary Embolism in the Emergency Department

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Abstract

Objectives: Pregnancy causes a small increase in risk of venous thromboembolism (VTE), but a large increase in concern upon presentation to an emergency department (ED) with symptoms of pulmonary embolism (PE), which may cause physicians to employ a low test threshold. This was a systematic review with the hypothesis that symptomatic pregnant patients in the ED have a low relative risk (RR) for VTE outcome.

Methods: Studies in all languages were identified by structured search of PubMed, EMBASE, the Cochrane library, and bibliographies in February 2014. Papers with ED patients evaluated for possible PE that included pregnancy status, and had adequate reference standards, were included. An outcome of VTE (either deep venous thrombosis [DVT] or PE) was considered disease-positive (VTE+). Papers were assessed for selection and publication bias, and heterogeneity (I^2). The random effects model was used if $I^2 > 24\%$.

Results: Seventeen full-length studies of 25,339 patients were analyzed. Pooled data showed $I^2 = 0\%$ with a symmetrical funnel plot. Two small studies with less than 1% of all patients had evidence of selection bias. The frequency of VTE+ rate among the 506 pregnant patients was 4.1% (95% confidence interval [CI] = 2.6% to 6.0%), compared with 12.4% (95% CI = 9.0% to 16.3%) among nonpregnant patients. The pooled RR of pregnancy for VTE+ diagnosis was 0.60 (95% CI = 0.41 to 0.87). Patients in the third trimester had a RR of 0.85 (95% CI = 0.40 to 1.77), and patients of childbearing age (≤45 years) had a RR of 0.56 (95% CI = 0.34 to 0.93).

Conclusions: In the ED setting, physicians test for PE in pregnant patients at a low threshold, resulting in a low rate of VTE diagnosis and a RR of VTE that is lower than that for nonpregnant women of childbearing age who are tested for PE in the ED setting.

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A pregnant woman who presents to an emergency department (ED) with signs or symptoms of possible pulmonary embolism (PE) poses a difficult diagnostic challenge for the clinician, who must balance the need to avoid radiation and contrast exposure to the mother and fetus, against the specter of missing a PE diagnosis that, left untreated, could cause harm to two patients simultaneously.[1] Decision-making is complicated by the fact that pregnancy increases risk of clotting and causes physiologic changes that to some

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extent mimic those of PE, including dyspnea, leg swelling, and an increased resting heart rate. Pregnancy also increases the plasma D-dimer level, thus complicating its use as a rule-out test.[2–4] The influences of traditional medical teaching and the practice of grouping the risk of deep venous thrombosis (DVT) and PE together for pregnant patients, added to the emotional consequences of missing PE in pregnancy, may prompt clinicians to initiate the diagnostic process for PE in pregnant patients at an exceedingly low test threshold. Indeed, pregnancy is absent as a criterion in all structured clinical decision rules for PE.[5,6]

Clinicians may perceive that pregnant patients have a high risk of PE because epidemiologic data show that pregnancy and the postpartum state increase a woman's risk of venous thromboembolism (VTE), including PE and DVT. However, if these data are analyzed by removing women who were postpartum, or who had isolated DVT, then the absolute risk for PE in pregnancy is relatively small. In Olmsted County, Minnesota, Heit et al.[7,8] found the rate of diagnosed PE in pregnant patients was 32/100,000, which is about the same as for all women under 40 years of age in the same region. In the United Kingdom, Sultan et al.[9,10] found the overall rate of VTE (including both DVT and PE) was 20/100,000 person-years among women of childbearing age, compared with 55/100,000 person-years for pregnant women with one risk factor for VTE. In contrast, Sultan et al. reported that the rate of VTE was 421/100,000 person-years in the early postpartum period.[9] In a meta-analysis of 23 epidemiologic studies, Meng et al.[11] found that 70% of all PEs diagnosed during the entire course of pregnancy and delivery occurred postpartum and that PE occurs in only three out of 10,000 pregnancies. Thus, we hypothesize that emergency physicians may overestimate the risk of VTE in pregnant patients with symptoms of PE and therefore order diagnostic testing liberally, resulting in a low outcome rate of VTE.

To test this hypothesis, we aimed to measure the outcome rate, or prevalence, of VTE among ambulatory pregnant patients tested for PE and to compare this prevalence to the VTE rate among nonpregnant patients. To accomplish this we conducted a systematic literature review and meta-analysis to quantify the rate of diagnosis and relative risk (RR) for VTE among symptomatic pregnant patients tested for PE.

METHODS

The main question of this work was to determine the pooled prevalence of VTE in symptomatic pregnant ED patients for whom clinicians order a diagnostic test for PE, to inform discussion about the test threshold that clinicians are currently using to order a diagnostic test for pregnant patients with symptoms of PE. The test threshold represents the lowest pretest probability at which clinicians decide to order a diagnostic test.[12] For PE, it has been well established that pretest probability is arithmetically linked to the posttest probability using the likelihood ratio for the diagnostic strategy.[6] Therefore, assuming the inclusion of studies that employed reference standards that produce narrow likelihood ratio negative ranges, the rate of positive VTE diagnosis (VTE+) and the RR of pregnancy will reflect the test threshold. The methodology used follows that recommended by the MOOSE standardized reporting guidelines.[13]

Literature Search

In February 2014, we performed a systematic search of MEDLINE, the Cochrane library, and EMBASE for studies that examined ED samples of patients evaluated for suspected PE that did not exclude pregnant patients. The methods were registered at http://www.crd.york.ac.uk/PROSPERO/. We first established a search strategy likely to find relevant studies of PE diagnosis. We used sequential search strategies in MEDLINE using PubMed designed to capture studies of diagnosis, diagnostic accuracy, and outcomes. We used the following independent search strategies, abbreviated here for clarity: PE and: Emergency; Diagnosis; Diagnostic accuracy; Outcomes; Pregnancy; D-dimer. With assistance from a medical librarian, we searched EMBASE using three concept groups: PE, emergency medicine, and risk/accuracy/predictive value/incidence, while precluding entry of duplicate citations. The details of these search strategies are shown in Data Supplement S1 (available as supporting information in the online version of this paper).

Other sources included a search of the Cochrane library database using the term *embolism. We also searched the bibliographies of meta-analyses and book chapters on topics relevant to PE diagnosis: clinical decision rules,[6,14,15] D-dimer,[16,17] clinical pathways and guidelines,[18–21] and other diagnostic methods.[22–24] In addition, we queried www.clinicaltrials.gov for studies involving pregnancy and e-mailed known researchers in the field to find so-called gray-zone or fugitive literature.

Two authors (DMR and JAK) reviewed the results of the search for relevance and independently read the titles and abstracts of all retrieved citations. The inclusion criteria were: studies of symptomatic ED patients who underwent objective diagnostic testing for PE which included data on risk factors for VTE. We assessed interobserver reliability with Cohen's kappa. The same two authors independently read the retained full-length articles for the following criteria: evidence of inclusion of women of childbearing age and the possibility that pregnancy status may have been collected and evidence of a prospective or retrospective diagnostic algorithm with a predefined reference standard for PE that included at least either pulmonary vascular imaging or mixed-objective testing, plus clinical outcomes assessed >30 days after evaluation. Exclusion criteria included the written statement that pregnant patients were excluded; those studies that clearly indicated the data were nonadditive (i.e., redundant with previously published data) and including secondary analyses of other published data. Discordances were resolved by consensus with a third author (MT) as arbitrator. For papers that reported outcomes of DVT and PE separately, we report the outcome of either diagnosis (VTE) within 90 days. To calculate the RR, each study had to report the rate of VTE diagnosis among those patients who were pregnant and among those who

were not. We also recorded the outcomes of patients with third-trimester status when these data were available. When necessary, we e-mailed the corresponding authors for these data up to three times. Studies that did not include pregnancy data and had no author clarification were excluded.

We graded study quality using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2), using a standard form.[25] Because we were studying the RR of a clinical feature, as opposed to the diagnostic accuracy of a test, we did not consider domain 2 (index testing) of QUADAS as relevant. Each study was graded as "low risk," "high risk," or "unclear risk" for bias in terms of selection of patients and reference standard. For patient selection, we considered a study low risk if it enrolled patients under conditions similar to what an emergency physician is likely to experience in evaluating a symptomatic patient in the ED without preselection by a physician, a diagnostic test, or clinical selection criteria. We considered patient selection bias at high risk if the paper or personal communication with the author indicated that any of these preselection criteria were applied prior to data collection. We considered the reference standard at low risk of bias if all patients had either pulmonary vascular imaging or D-dimer test and clinical follow-up at >45 days that was free of VTE. Studies without these criteria had high-risk reference standards. Studies lacking sufficient criteria to understand patient selection or reference standard had unclear risk. The reference standard for VTE– status required use of a test known to produce a likelihood ratio negative less than 0.20, including one of the following: negative quantitative D-dimer result together with negative clinical follow-up performed >30 days after enrollment, diagnostic negative scintillation lung scan result interpreted according to well-accepted criteria, or negative computerized tomographic pulmonary artery (CTPA) scanning.[16,20,26] We considered diagnosis of VTE+ to include either PE or DVT because most studies of diagnostic accuracy consider a diagnosis of DVT made in a patient with symptoms of PE as tantamount to a diagnosis of PE.[20] The reference standard for VTE+ diagnosis required any of the following incident within 90 days of enrollment: diagnostic high-probability ventilation perfusion lung scanning, positive CTPA scan, positive formal pulmonary angiography, positive autopsy for PE, or DVT confirmed with compression ultrasonography or magnetic resonance imaging.

Data Analysis

For included studies, we generated a table of total number of nonpregnant patients (females and males), the number that were VTE+, and total number with pregnancy-related VTE. We also recorded the same data for postpartum status. The primary comparison was the RR for VTE+ among pregnant patients by comparing the proportions of VTE+ pregnant patients to nonpregnant patients. We assessed for heterogeneity between studies using Cochran's Q-test ($p < 0.05$) or the inconsistency index (I^2). We screened for publication bias using the test of Egger for asymmetry of the funnel plot.[27] We report the RR from the random-effects model and the fixed-effects RR only if heterogeneity was low ($I^2 < 25\%$).[28] Unless otherwise stated, all reported confidence intervals (CIs) are from the random effects model.

We performed two sensitivity analyses: we removed studies with selection bias, and we compared studies drawn from American versus populations from other countries, because prior work found a significantly lower rate of VTE diagnosis in American ambulatory populations with suspected PE than is found in European countries.[29] We tested the effect of trimester and age on RR in two subgroup analyses: the RR the third trimester of pregnancy and the VTE+ rate and the RR for pregnant patients compared with nonpregnant patients of childbearing age (age ≤ 45 years).[7,8]

RESULTS

The search revealed 2,816 titles and abstracts that were screened for relevance by two independent reviewers, yielding a good combined interobserver reliability for retained studies ($\kappa = 0.80$; 95% CI = 0.77 to 0.83). Figure 1 shows the selection process and Data Supplement S2 (available as supporting information in the online version of this paper) shows the breakdown of results by each search term. Of 178 full-length papers and 17 abstracts that were retained for review by two authors, 161 were excluded for the reasons in Data Supplement S2, leaving 17 full-length papers and two abstracts for data abstraction. To obtain additional information, we e-mailed 56 authors which returned error messages in nine cases, no response from 21, and definitive responses from 26 (46%). Authors replied that pregnant patients were excluded ($n = 3$) or that no pregnant patients were enrolled or additional pregnancy data were not recorded ($n = 20$) or provided additional data on outcomes of pregnant patients already mentioned in the tables of published reports ($n = 3$).[30–33] One author also informed us that an additional case-control study that included pregnant patients evaluated for PE was in peer review, and www.clinicaltrials.gov revealed one clinical trial (NCT00771303) relevant to the subject matter. Two authors (JAK and MPT) provided supplemental data from 11 publications using their own databases.[5,34–43]

Two readers had perfect agreement on their choices of 17 retained full-length papers and two abstracts (Table 1). All 17 full-length papers studied unselected emergency patients with suspected PE, including nonpregnant and pregnant patients, whereas both abstracts included only pregnant patients, and their results are included in the sensitivity analysis.[44,45]

Assessment for Bias

Table 1 describes the relevant domains of each study that might affect bias, including the setting, patient selection process, and reference standard. All studies had adequate reference standards, but two studies were deemed high risk for selection bias from prescreening with risk stratification or diagnostic testing. These two studies combined represented only 1% of the total number of patients. We note that no studies explicitly stated an enrollment requirement for pregnancy testing but all authors contacted indicated that pregnancy testing was mandated prior to pulmonary vascular imaging at their

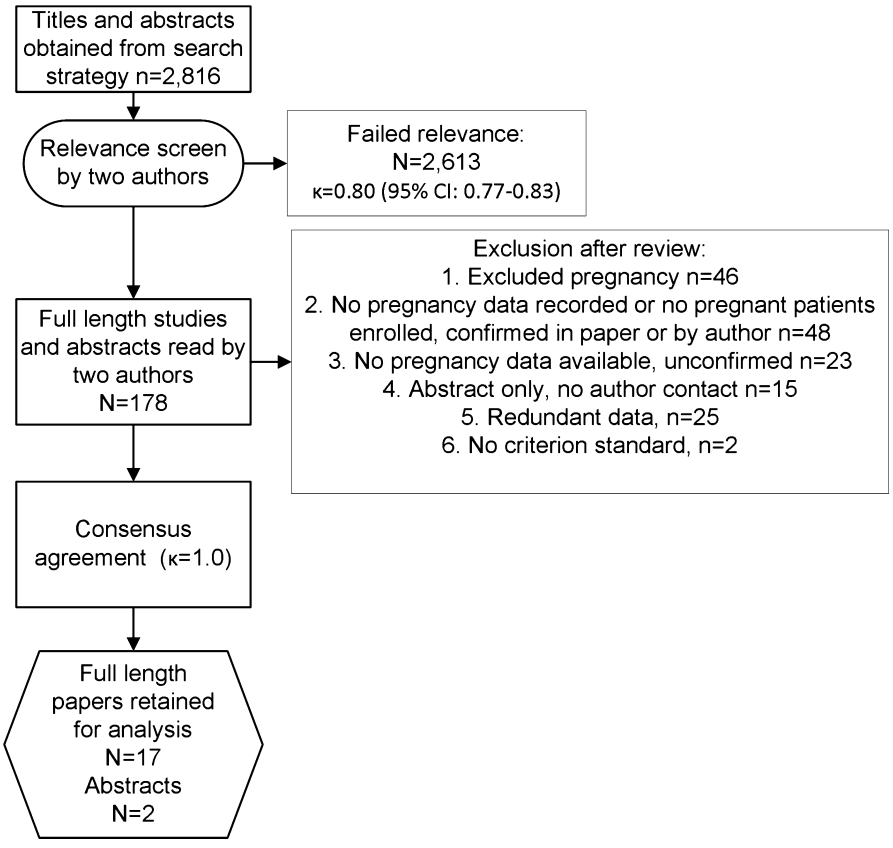


Figure 1. Flow diagram of included studies.

centers. For the main study question (RR of pregnancy), pooled data showed minimal heterogeneity [Cochran Q 12.2 (df = 15) p = 0.65; I^2 = 0% (95% CI = 0 to 46)] and a relatively symmetrical funnel plot (Egger intercept = –0.25; 95% CI = –1.5 to 1.0; p = 0.66; Figure 2). Eleven studies comprising 14,782 (or 58%) of the patients came from studies on which an author of this work was a primary author and we confirm that each of these represented unique patients with no duplication.

Frequency of Evaluation of Pregnant Patients

Table 2 summarizes the number of patients based on pregnancy and VTE status for each included study. The 17 full-length studies included 25,339 subjects evaluated for PE in the ED, including 2,636 who had VTE (13%, 95% CI = 10% to 17%). A total of 506 patients were pregnant, representing 2.0% of all patients (95% CI = 1.5% to 2.6%, range = 0.7 to 4.6). All 506 pregnant patients underwent pulmonary vascular imaging.

RR of VTE+ Outcome in Pregnant Patients With Suspected PE

The forest plot in Figure 3 shows the main study question, namely the RR of pregnancy on VTE+ diagnosis in symptomatic ED patients evaluated for PE. The random-effects model found the RR was 0.60 (95% CI = 0.41 to 0.87, I^2 = 0%), and the fixed-effects RR was 0.45 (95% CI = 0.30 to 0.68).

The frequency of VTE+ diagnosis among 24,833 nonpregnant patients was 12.4% (95% CI = 9.0% to 16.3%, I^2 = 0%), and the frequency of VTE+ diagnosis among the 506 pregnant patients was 4.1% (95% CI = 2.6% to 6.0%, I^2 = 0%). The forest plots of these data are shown in Figure 4.

Sensitivity Analyses. 1) Exclusion of the two small studies with evidence of selection bias produced a prevalence of VTE in nonpregnant patients of 10% (95% CI = 6% to 15%), a prevalence of VTE in pregnant patients of 3.7% (95% CI = 2.1% to 5.7%), and a pooled RR of 0.50 (95% CI = 0.32 to 0.78; I^2 = 0%). 2) Twelve studies with patient samples taken only from the ultrasound included 18,572 patients, which had a pooled proportion of pregnant patients of 2.1% (95% CI = 1.5% to 2.8%; I^2 = 84%), a pooled rate of VTE+ diagnosis of 3.5% (95% CI = 2.0% to 5.5%; I^2 = 0%), and a pooled random effects RR of 0.50 (0.30 to 0.83; I^2 = 0%).[5,30,31,34–39,43,46,47] 3) The five non-US full-length studies included 6,767 patients with a pooled proportion of pregnant patients of 1.5% (95% CI = 0.9% to 2.3%; I^2 = 70%), a pooled rate of VTE+ diagnosis of 8.2% (95% CI = 1.5% to 29.7%; I^2 = 97%), and a pooled random-effects RR of 0.61 (95% CI = 0.27 to 1.39; I^2 = 57%).[40–42,48,49] 4) Inclusion of the two abstracts of exclusively pregnant patients (n = 239), which were both performed in Europe in the nonultrasound analysis, resulted in a RR of 0.36 (95% CI = 0.13 to 0.99).[44,45]

Subgroup Analyses. 1) Authors had access to original data for six studies to calculate the RR specific to the third trimester of pregnancy.[5,34,36,38,40,49] These six studies together included 117 (47%) patients in the third

Table 1
Description of Included Studies

Citation	City/Country	Setting	Patient Selection	Risk of Selection Bias*	Minimum Reference Standard	Risk of Imperfect Criterion Standard Bias†
Kline et al.[34]‡	Charlotte, NC; and Royal Oak, MI	Data from three published studies of PE diagnosis from two sites	Nonselected ED patients undergoing testing for PE	Low	V/Q scanning with follow-up	Low
Kline et al.[35]	Charlotte, NC	Data from a clinical pathway at one center	Nonselected ED patients undergoing testing for PE	Low	D-dimer with follow-up	Low
Kline and Hogg[36]‡	Charlotte, NC	Single-center study of diagnostic accuracy	Nonselected ED patients undergoing testing for PE	Low	All had CTPA scanning with follow-up	Low
Kline et al.[37]‡	Charlotte, NC	Single-center study of diagnostic accuracy	Nonselected ED patients undergoing testing for PE	Low	D-dimer with follow-up	Low
Roy et al.[41]‡	France, Belgium	Multicenter study of diagnostic appropriateness	Nonselected ED undergoing testing for PE	Low	D-dimer with follow-up	Low
Runyon et al.[38]‡	Charlotte, NC	Single-center study of diagnostic accuracy	Nonselected ED patients undergoing testing for PE	Low	D-dimer with follow-up	Low
Nordenholz et al.[39]‡	Charlotte, NC; and Denver CO	Two-center study of diagnostic accuracy	Nonselected ED patients undergoing testing for PE	Low	D-dimer with follow-up	Low
Turedi et al.[48]	Trabzon, Turkey	Single-center study of diagnostic accuracy	Preselected ED patients undergoing testing for PE	High	All had CTPA scanning with follow-up	Low
Than et al.[40]‡	Christchurch, NZ	Single-center study of diagnostic accuracy; data from manuscript supplemented by author	Nonselected ED patients undergoing testing for PE	Low	D-dimer with follow-up	Low
Roy et al.[42]‡	France	European multicenter study of two diagnostic algorithms	Nonselected ED undergoing testing for PE	Low	D-dimer with follow-up	Low
Crichlow et al.[30]	Philadelphia, PA	Single-center study of outcome	Nonselected ED patients undergoing testing for PE	Low	All had CTPA scanning with follow-up	Low
Kline et al.[43]‡	Four cities, United States	Four-center study of diagnostic accuracy	ED and inpatients with suspected PE; only ED patients retained for analysis	Low	All had CTPA scanning with follow-up	Low
Courtney et al.[5]‡	12 cities, United States	American multicenter sample from an outcomes study	Nonselected ED patients undergoing testing for PE	Low	D-dimer with follow-up	Low
Dresden et al.[46]	Boston, MA	Single-center study of diagnostic accuracy	ED patients with Well's score > 2 undergoing testing for or with confirmed PE	High	All had CTPA or V/Q scanning	Low
Shujaat et al.[47]	Jacksonville, FL	Single-center study of care process	Retrospective study of patients who underwent CTPA	Low	All had CTPA scanning with chart review	Low
Adams et al.[31]	Utah	Multicenter study of care process	Retrospective study of patients who underwent CTPA	Low	All had CTPA scanning with chart review	Low
Hogg et al.[49]	Manchester, England	Single-center study of diagnostic accuracy	Outpatients evaluated for PE only provided by author	Low	D-dimer with follow-up	Low
Sonde et al.[44] (abstract)	Manchester, England	Single-center study of outcome; abstract only, no contact details	All patients pregnant	Unclear	Unclear	Unclear
Nijkeuter et al.[45] (abstract)	Three cities, Netherlands	Three-center study of CTPA in pregnancy	All patients pregnant	Unclear	All had CTPA scanning with follow-up	Unclear

CTPA = computed tomography pulmonary angiography; PE = pulmonary embolism; V/Q = ventilation/perfusion.
*Low risk = included nonselected sample of pregnant and nonpregnant patients enrolled in the early stages of evaluation of suspected PE; high risk = patients preselected by physician referral, or both risk stratification and diagnostic testing.
†Low risk= Pulmonary vascular imaging or D-dimer with follow-up > 30 days; HIGH risk= all others.
‡Indicates studies for which authors had access to original data

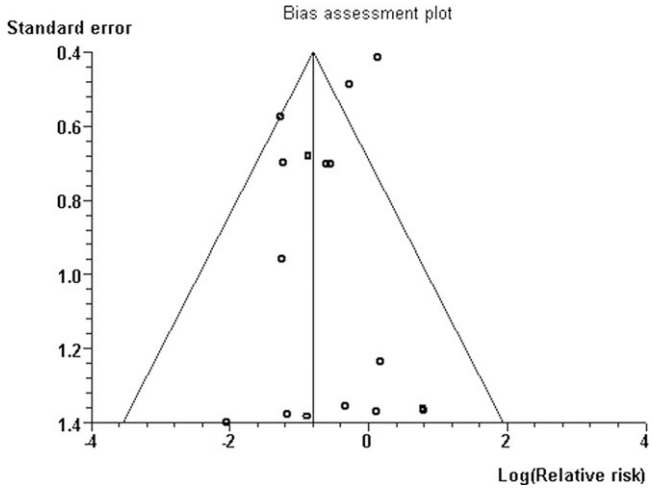


Figure 2. Funnel plot of the RR of VTE outcome for pregnant patients compared with nonpregnant patients for the 17 included studies. RR = relative risk; VTE = venous thromboembolism.

trimester, of whom four (3.4%, 95% CI = 1% to 7.5%) were VTE+, and 13,458 nonpregnant patients, of whom 1,118 (8.3%, 95% CI = 7.5% to 15.5%) were VTE+. From this sample, the RR of third-trimester pregnancy was 0.85 (95% CI = 0.40 to 1.77, random effects). 2) Authors had access to original data for 11 studies to calculate the VTE+ rate and RR specific to patients of childbearing age.[5,34–43] This included 8,130 nonpregnant patients aged ≤ 45 years, of whom 491 were VTE+ (6.2%, 95% CI = 3.9% to 9.0%), compared with 413 pregnant patients (age range 18 to 45 years), of whom 13 were VTE+ (3.7%, 95% CI = 2.1% to 5.7%), resulting in I^2 = 0% (95% CI = 0% to 54.4%), a random-effects RR of 0.67 (95% CI = 0.41 to 1.11), and a fixed-effects RR of 0.56 (0.34 to 0.93).

DISCUSSION

This systematic literature review and meta-analysis of 25,339 patients found that among symptomatic ED patients selected for testing for PE, approximately 2% were pregnant, and when compared with nonpregnant patients, the pregnant patients had a RR for VTE+ outcome of 0.60, significantly less than 1 (95% CI = 0.41 to 0.87, random effects). The rate of VTE+ diagnosis from 24,839 nonpregnant patients was 12.4% compared with a lower rate of VTE+ diagnosis in pregnant patients of 4.1% (95% CI = 2.6 to 6.0). The outcome rate of VTE+ in pregnant patients was within the 3% to 5% range for VTE+ outcome that can be expected for patients with a low pretest probability from a validated clinical decision rule.[6] We believe that these findings challenge the common belief that pregnancy should be considered a categorically high-risk condition in the initial approach to a patient with possible PE. This is important because overinvestigation for PE has negative health effects.[50,51]

The major strengths of this work are the large number of patients, the lack of evidence of heterogeneity or publication bias for the RR calculation, and the fact that the authors had access to patient-level data in the majority of studies, permitting sensitivity and subgroup calculations that bolster the assertion that pregnancy does not confer a high risk of VTE outcome. First, in a

Table 2
Data From Included Studies

					VTE+			
Citation	All	Nonpregnant Patients	Pregnant Patients	Third Trimester	Total	Nonpregnant	Pregnant	Third Trimester
Kline et al.[34]	934	910	24	3	181	181	2	0
Kline et al.[35]	1,339	1,278	61	—	77	77	2	—
Kline and Hogg[36]	178	174	4	3	24	24	0	0
Kline et al.[37]	2,302	2,231	71	—	108	108	2	—
Roy et al.[41]	1,529	1,517	12	—	442	441	1	—
Runyon et al.[38]	1,193	1,188	5	2	45	45	0	0
Nordenholz et al.[39]	304	299	5	—	22	22	0	—
Turedi et al.[48]	130	127	3	—	75	75	2	—
Than et al.[40]	3,224	3,162	62	50	269	269	4	4
Roy et al.[42]	1,645	1,626	19	—	313	313	0	—
Crichlow et al.[30]	152	149	3	—	8	8	0	—
Kline et al.[43]	353	345	8	—	46	46	0	—
Courtney et al.[5]	7,940	7,792	148	54	561	561	3	0
Dresden et al.[46]	146	145	1	—	30	30	0	—
Shujaat et al.[47]	231	228	3	—	48	0	0	—
Adams et al.[31]	3,500	3,430	70	—	340	338	2	—
Hogg et al.[49]	239	232	7	5	47	47	0	0
Subtotal (Full-length papers)	*25,339*	*24,833*	*506*	*117*	*2,636*	*2,272*	*18*	*4*
Sonde et al.[44]*	90	0	90	—	5	0	5	—
Nijkeuter et al.[45]*	149	0	149	—	6	0	6	—
Total all studies	*25,578*	*24,822*	*745*	*117*	*2,647*	*2,272*	*29*	*4*

VTE = venous thromboembolism.
*Abstracts only, included in sensitivity analysis.

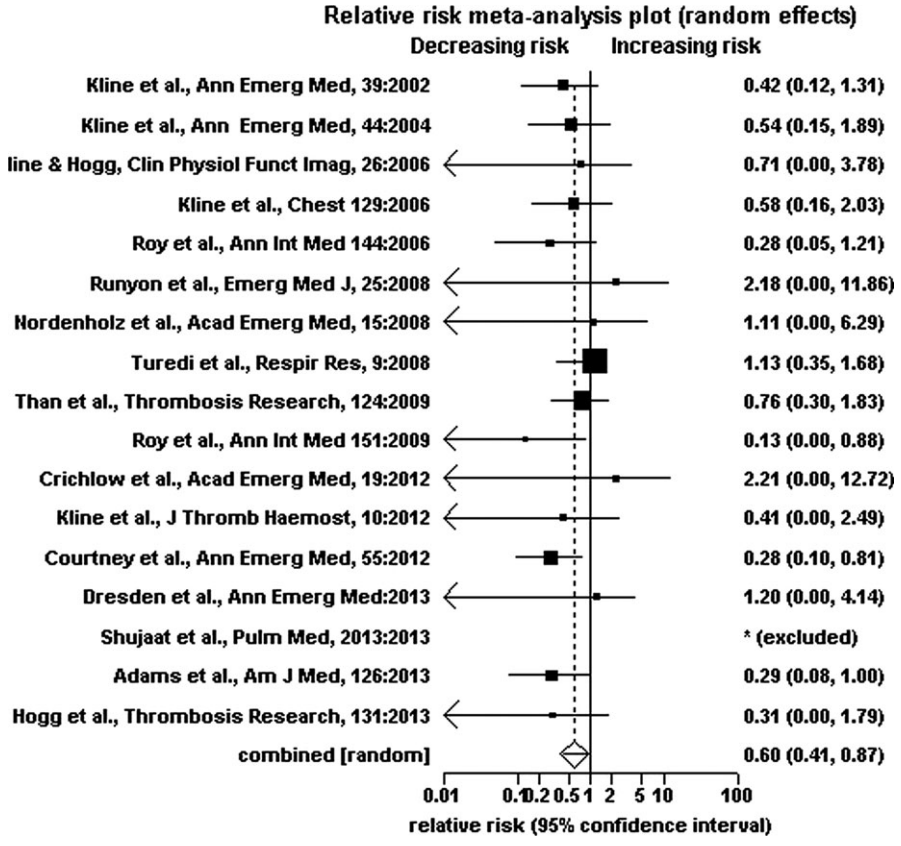


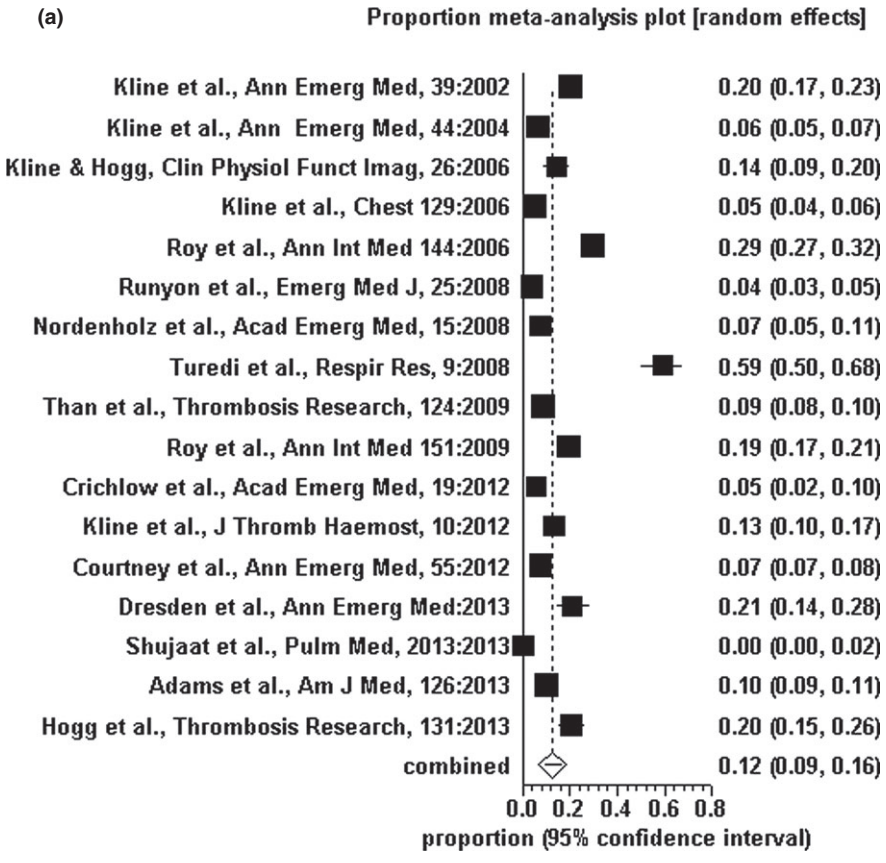
Figure 3. Relative risk of pregnancy for diagnosis of venous thromboembolism (random effects model).

sensitivity analysis from 11 studies, the RR of pregnant status remained low ($I^2 = 0\%$, fixed-effects RR of 0.56, 95% CI = 0.34 to 0.93) when compared with nonpregnant patients of childbearing age. For the sensitivity analysis that examined non-US studies, the RR was similar (0.61), but the upper limit of the 95% CI was above unity (95% CI = 0.27 to 1.39). Sparse data were available from third trimester patients, resulting in a RR and relatively wide 95% CIs 0.85 (95% CI = 0.40 to 1.77) that include the possibility that third-trimester pregnancy increases risk among patients presenting to the ED.

We do not interpret these data to indicate that pregnant patients have a lower risk of PE when compared to healthy nonpregnant patients. Instead, we believe that our data illustrate that clinicians order testing at a low test threshold among pregnant patients. The evaluation of a pregnant patient with signs and symptoms of PE in the emergency setting obligates clinicians to consider a complex mix of information that often causes decisional conflict. Pregnancy clearly represents a population risk factor for VTE, but at the same time, most pregnant patients are relatively healthy compared with nonpregnant patients undergoing testing for PE. In their training, clinicians may be taught that PE is the most, or one of the most, common treatable causes of maternal death. Expert guidelines and book chapters clearly state that PE can only be diagnosed or excluded with reasonable certainty by pulmonary vascular imaging.[19,24] Yet, the clinician's decision of how to test affects two vulnerable subjects, and excessive testing could harm the fetus by exposing it to ionizing radiation; neonatal hypothyroidism remains a possibility because non–ion-iodinated contrast crosses the placenta.[52–54] Radiation from CTPA to the female breast may increase risk of cancer.[55] Exclusion of PE with nonionizing means, such as decision rules and a D-dimer level, is confounded by the lack of data in pregnant patients and that pregnancy naturally elevates the plasma D-dimer concentration, rendering D-dimer inefficient as a screening tool by the third trimester because the D-dimer concentration exceeds the standard threshold in nearly all women in the third trimester, even with normal pregnancy.[3,4] Within this context of conflicting rationale, our data open the possibility that pregnant patients could be safely excluded using existing decision rules coupled with a threshold-adjusted D-dimer level, or following a protocol whereby bilateral lower extremity compression ultrasonography is the initial diagnostic test, as has been suggested by Pahade et al.,[56] although this approach has not been tested.

LIMITATIONS

The most likely factor that might change our findings would be data from studies that included pregnant patients that we missed. We minimized this threat to validity by using broad search term criteria to locate studies of ED patients that might have included pregnant patients. However, we recognize that unlike a typical meta-analysis of diagnostic accuracy, which aggregates data from studies performed to examine a specific test, we aggregated supporting data to assess



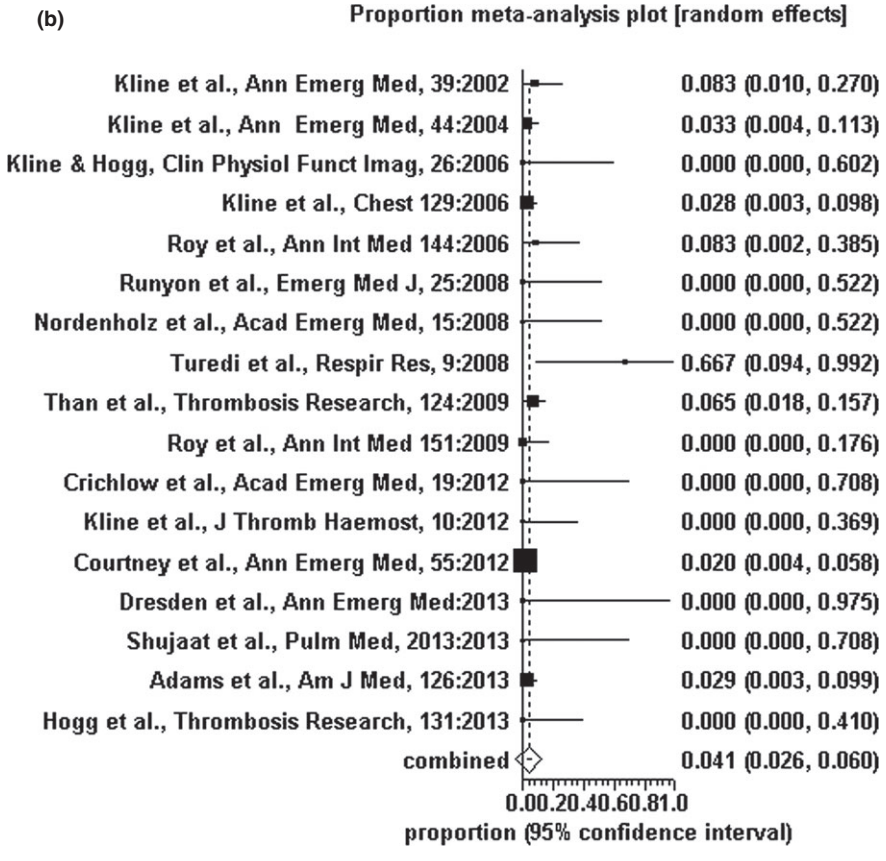


Figure 4. Frequency of diagnosis of venous thromboembolism in (A) nonpregnant and (B) pregnant patients.

predictive value of a patient phenotype. Most articles did not report the breakdown of data required for meta-analysis, namely the number of nonpregnant and pregnant patients with and without VTE. To further minimize the risk of missing data, we e-mailed 56 authors on numerous occasions to ask if they recorded pregnancy data. Among the 26 authors who responded, all but three indicated that they either excluded pregnancy or could not tell us pregnancy status. For the three who responded with new data, their published works had indicated the numbers of pregnant patients that were included, but did not state their VTE status.[30–33] However, in no case did an author inform us that he or she collected pregnancy data, but reported none of these data in the resulting article.

CONCLUSIONS

This systematic review and meta-analysis of 25,399 patients found that symptomatic pregnant ED patients tested for pulmonary embolism had a low outcome rate of venous thromboembolism and a relative risk for venous thromboembolism diagnosis that was lower than that for nonpregnant ED patients, including a subgroup analysis of patients of childbearing age. These findings challenge the common belief that pregnant patients with symptoms of pulmonary embolism are at high risk for pulmonary embolism diagnosis.

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Search strategies used in February 2014 to locate papers relevant to the diagnosis of samples of patients, including pregnant patients, undergoing testing for pulmonary embolism in the ED.

Data Supplement S2. Results of search, screen, and review processes.