The diagnostic management of suspected pulmonary embolism

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Diagnosis of deep vein thrombosis and pulmonary embolism in pregnancy; a systematic review

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Abstract

Introduction

Diagnosing deep vein thrombosis (DVT) and pulmonary embolism (PE) in pregnancy is challenging. Many of the common diagnostic tests, including compression ultrasonography (CUS), ventilation-perfusion scintigraphy (VQ scan) and helical computed tomography (hCT) that have been extensively investigated in non-pregnant patients, have not been appropriately validated in pregnancy. Extrapolating results of diagnostic studies of DVT and PE in non-pregnant patients to those who are pregnant may not be correct because during pregnancy, physiologic and anatomic changes may affect diagnostic test results, presentation and natural history of VTE.

Methods

We performed a systematic analysis of published studies addressing accurate diagnostic testing for DVT and PE in pregnancy to determine the accuracy of these tests in pregnancy.

Results

Our initial search yielded 530 articles of which four remained for inclusion, three studies investigating diagnostic testing in patients with a clinical suspicion of DVT and one study in patients with a clinical suspicion of PE.

Conclusions

From our systematic analysis of published studies investigating diagnostic testing for a clinical suspicion of DVT or PE in pregnancy we conclude that; 1) two studies support withholding anticoagulant therapy in pregnant women with a clinical suspicion of DVT and normal results on serial IPG (impedance plethysmography), however, IPG is no longer used; 2) one study demonstrated that a normal CUS at presentation combined with a normal D-dimer test or an abnormal D-dimer test combined with normal serial CUS appears promising for safely excluding DVT in pregnant patients, but too few patients were included in this pilot-study to draw firm conclusions; and 3) one study investigated pregnant patients with a clinical suspicion of PE and this study concluded that in patients with normal or non-diagnostic VQ scans, withholding anticoagulant therapy might be safe, but this needs confirmation in larger studies. Recommendations on diagnostic testing of pregnant patients with a clinically suspected DVT or PE are provided.

Introduction

Diagnosing deep vein thrombosis (DVT) or pulmonary embolism (PE) in pregnancy presents challenges to clinicians. Non-thrombotic leg or respiratory symptoms are commonly experienced in pregnancy and are often clinically indistinguishable from those found in patients with DVT and PE. Hence, the clinical diagnosis is inaccurate and accurate diagnostic testing is essential to exclude or diagnose venous thromboembolism (VTE). However, many of the common diagnostic tests including compression ultrasonography (CUS), ventilation-perfusion scintigraphy (VQ scan) and helical computed tomography (hCT), that have been extensively investigated in non-pregnant patients, have not been appropriately validated in pregnancy. Extrapolating results of diagnostic studies of DVT and PE in non-pregnant patients to those who are pregnant may not be correct because of physiologic changes during pregnancy and the possibility of differences in pathophysiology and presentation of VTE in pregnancy. Also, studies of non-pregnant patients invariably report on subjects who are, on average, older and are more likely to have co-morbid cardio-respiratory conditions that can result in an abnormal VQ scans.
The purpose of this review is to establish the evidence concerning the accuracy of diagnostic tests performed for a clinical suspicion of PE and DVT during pregnancy. Therefore, we undertook a systematic analysis of published studies addressing diagnostic testing for DVT and PE in pregnancy. Further, recommendations for diagnostic testing are made for clinicians when they evaluate pregnant patients with clinically suspected DVT or PE.

Methods

Search strategy

We used electronic search strategies to identify relevant studies. The following electronic databases were searched: PubMed (1966 to November 2004), EMBASE (1980-nov 2004), Cochrane, the Library Issue 1, 2005 and Web of Science using the search terms *pregnancy, gestational period, pulmonary embolism, venous thrombosis, deep vein thrombosis, radiological tests, diagnosis, pulmonary angiography, helical or spiral computed tomography, ventilation-perfusion lung scintigraphy, magnetic resonance imaging, compression ultrasound, impedance plethysmography* and *venography*. We augmented our search by reviewing the reference lists of retrieved articles. Studies published in any language were used.

Study selection

We attempted to identify all published clinical studies that evaluated pregnant patients with a clinical suspicion of deep vein thrombosis or pulmonary embolism. Of potentially eligible articles, abstracts were read to determine eligibility and in case of doubt, full-text articles were retrieved. To be included, a study had to 1) involve consecutive pregnant patients with a clinical suspicion of DVT or PE; 2) use validated diagnostic tests to diagnose DVT (CUS or impedance plethysmography (IPG) or venography for a suspicion of DVT or magnetic

resonance imaging for a suspicion of iliac vein thrombosis) and PE (pulmonary angiography or hCT, or VQ lung scanning); 3) use validated diagnostic testing in patients with suspected VTE in follow up; 4) describe a pre-specified duration of follow-up of patients with negative tests; and 5) withhold anticoagulant treatment in patients with negative tests.

Data extraction

Two investigators independently assessed studies for inclusion according to the predefined methodological criteria. Investigator disagreements were resolved by majority opinion of a third investigator.

Results

Our initial search identified 530 articles, of which 14 were potentially eligible for analysis[1-14]. According to the predefined inclusion criteria, 10 of the 14 studies were excluded (Table 1). Reasons for exclusion were: consecutive patients were not evaluated[5;6;10], only patients with confirmed instead of suspected DVT were included [1;2;7;8], objective testing was not performed in all patients[2;10] and no pre-specified duration of follow-up of patients with negative tests was stated [2-6;9;10]. Therefore, four studies were included in the primary analysis, three studies investigating diagnostic testing in patients with a clinical suspicion of DVT and one study investigating diagnostic testing in patients with a clinical suspicion of PE[11-14]. As there were so few studies, each study is briefly discussed.

Table 1
Excluded studies

Ref	Test(s) used	Patients	Nr of patients	no DVT/PE	Duration of follow-up and nr. of events in patients with normal tests
(1)	Venography, plethysmography, thermography	Confirmed DVT	17	0	not applicable
(2)	Clinical diagnosis	Suspicion of DVT	13	?	not described
	Venography, plethysmography	Confirmed DVT	30	0	not applicable
(3)	Venography	Suspicion of DVT	29	17	not described
(4)	CUS	Suspicion of DVT	28	21	not described
(5)	Doppler US	Suspicion of VTE	58	4	not described
(6)	Venography + color Doppler ultrasound	Suspicion of VTE	59	9	not described
(7)	Duplex, Venography or autopsy	Confirmed DVT or PE	32	0	not described
(8)	Doppler, IPG, venography, CT/MRI, VQ, PA	Confirmed DVT or PE	165	0	not described
(9)	MRI	Suspicion of Iliac thrombosis	10	7	not described, no VTE
(10)	VQ scintigraphy	Suspicion of PE	82	64	median 25 months (range 3-60 months), 2 events with IP VQ scan

CUS: Compression UltraSound, DVT: Deep Vein Thrombosis, IP: intermediate probability, IPG: Impedance Plethysmography, MRI: Magnetic Resonance Imaging, PE: Pulmonary Embolism, US: UltraSound, VQ: (ventilation) perfusion lung scintigraphy, VTE: Venous Thrombo-Embolism

Studies investigating diagnostic testing for a clinical suspicion of DVT in pregnancy

Two studies evaluated the clinical validity of negative results by serial IPG in pregnant patients with a clinical suspicion of DVT[11;12]. In the study of Hull et al, patients had serial testing on the day of presentation and days 3, 5 or 7, 10 and 14 when IPG remained normal[12]. Of 152 patients, 139 had normal results on serial IPG and none had VTE during follow-up (3 months postpartum, 0%; 95% confidence interval (CI), 0-2.6%). In the second study, of 77 obstetric patients (47 pregnant, 30 postpartum) with suspected DVT, 45 had normal serial IPG and none had VTE during a 6-month follow-up period (0%; 95%CI, 0-6%)[11].

One pilot study evaluated CUS in the diagnosis of DVT in pregnancy[13]. Two hypotheses were tested: 1) a normal CUS on the day of presentation combined with a normal SimpliRed D-dimer (SRDD) test and 2) an abnormal SRDD at presentation but with normal serial CUS would both reliably exclude DVT in symptomatic pregnant women. Based on the initial CUS and SRDD result, women were categorized into one of four groups and managed accordingly; 1) CUS normal, SRDD normal; clinical follow up until 6 weeks postpartum; 2) CUS normal, SRDD abnormal; CUS was repeated 3 and 7 days later and those with normal serial CUS were followed until 6 weeks postpartum; 3) CUS equivocal; venography was performed; 4) CUS positive; DVT was diagnosed. Of 53 included patients, 7 were diagnosed with DVT (13%, 95%CI: 5.5-25.3%). Group 1 comprised 31 patients and none of them developed objectively diagnosed VTE during follow-up (0%, 95%CI: 0-9.2%). Four of the 18 women in group 2 were diagnosed with DVT on serial CUS and of the remaining 14 patients, none developed VTE during follow-up (0%, 95%CI: 0.7-26.8%). The authors conclude that a normal CUS at presentation combined with a normal SRDD or an abnormal SRDD combined with normal serial CUS appears to safely exclude DVT in pregnant patients, but larger confirmatory studies are needed.

Based upon the results of our systematic review of published studies investigating diagnostic testing for a clinical suspicion of DVT, there is clearly a huge need for large prospective studies evaluating currently available and new tests for the diagnosis of DVT in pregnant women. Unfortunately, 2 of 3 studies involved evaluation of IPG, a test that is no longer performed. The use of CUS with or without D-dimer testing merits further evaluation.

Studies investigating diagnostic testing for a clinical suspicion of PE in pregnancy

Chan et al. retrospectively studied the distribution of lung scan results and safety of withholding anticoagulation therapy following a normal or non-diagnostic scan in pregnant women[14]. Eight of 121 cases (6.6%) were already receiving treatment for venous thromboembolism prior to VQ scanning. In the remaining 113, 83 (73.5%) scans were interpreted as normal, 28 (24.8%) as non-diagnostic and 2 (1.8%) as high probability. In the 104 women who did not receive anticoagulation therapy following lung scanning (80

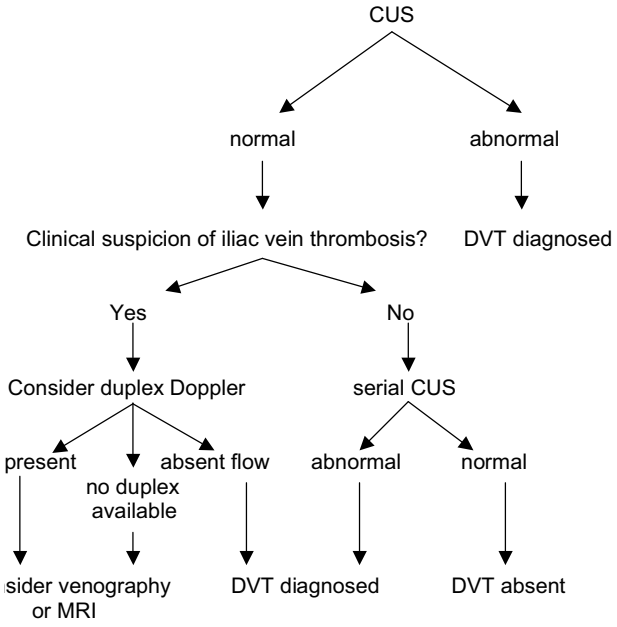
normal and 24 non-diagnostic), no venous thromboembolic events were reported during a mean follow-up period of over 20 months (0%, 95%CI: 0.0-1.0%). The authors conclude that the prevalence of high-probability VQ scans in pregnant women with suspected PE is very low. Withholding anticoagulation in pregnant women with normal perfusion scans is safe. Unfortunately, the small number of patients with non-diagnostic VQ scans and the fact that in non-pregnant patients, as many as 25% of patients with such scans have PE, do not allow us to conclude that PE can be excluded in a pregnant women with a non-diagnostic scan. Large prospective studies are needed to evaluate diagnostic strategies for pregnant women with suspected PE.

Based on the results of our systematic analysis of studies investigating diagnostic tests for a clinical suspicion of DVT or PE in pregnancy, there is dire need for properly designed studies of pregnant women with suspected DVT or PE. Consequently, the following recommendations for clinical practice regarding the diagnostic approach of a pregnant patient with a clinical suspicion of DVT or PE are partly driven by the personal opinion of the authors.

Recommended diagnostic testing of a clinical suspicion of deep vein thrombosis in a pregnant patient

Although there are no large, prospective studies evaluating CUS in pregnant patients for a clinical suspicion of DVT, there is no biologic reason why a clearly abnormal CUS wouldn't make a firm diagnosis of DVT. Therefore, compression ultrasonography should be performed as a first test in a pregnant patient with a clinical suspicion of DVT (Figure 1). Patients with an abnormal CUS, defined as a non-compressible segment of the popliteal or a more proximal vein can be diagnosed with DVT and should be treated appropriately with unfractionated or low molecular weight heparin. However, a normal CUS might not be as safe reassuring in non-pregnant patients since isolated iliac DVT is thought to be more common in pregnant than in non-pregnant patients and such thrombi are difficult to detect by CUS. Patients with a normal CUS should undergo serial CUS testing after day 6-8, or sooner – days 2 to 3 - when clinical suspicion is strong, to detect proximal extension of distal thrombi. If CUS becomes abnormal, DVT can be diagnosed. If doubt about the presence of DVT persists, limited venography with abdominal shielding should be considered. The amount of fetal radiation exposure with venography and abdominal shielding is less than 0.5 mSv (Table 2)[15]. This amount is much lower than the threshold dose for induction of malignancies (100 mSv) and justifies the use of diagnostic testing involving radiation in pregnancy for the exclusion of potentially fatal VTE[16;17]. If iliac or pelvic vein thrombosis is suspected, duplex Doppler ultrasound or full venography can be performed. In centres with availability of, and experience with MRI, MR venography is a reasonable alternative test to venography in demonstrating iliac or pelvic vein thrombosis. However, the safety of excluding DVT when MR venography is normal has not been demonstrated. The roles of pre-test probability assessment and D-dimer testing in the diagnosis of suspected DVT in pregnancy have yet to be defined.

Figure 1
Algorithm for a clinical suspicion of DVT in pregnancy



DVT: Deep Vein Thrombosis, CUS: Compression UltraSonography, MRI: Magnetic Resonance Imaging

Table 2
Radiation dose to the fetus by radiological examination

Diagnostic test	Radiation (mSv)
Unilateral venography without shielding	3.14
Unilateral venography with shielding	< 0.5
Pulmonary angiography via femoral route	2.21-3.74
Pulmonary angiography via brachial route	< 0.5
Perfusion scintigraphy(99mTc MAA, 200 MBq)	0.2-0.6
Perfusion scintigraphy (99mTc MAA, 40 MBq)	0·11-0·20
Ventilation scintigraphy (99mTc aerosol)	0.1-0.3
Ventilation scintigraphy (81mKr, 600MBq)	0·0001
Single-detector row helical CT	0·026
Multi-detector row helical CT	0·013

Estimates of radiation exposure are derived from McMaster University and University Medical Centre Leiden(15,17)
To convert mSv to rads: 1 mSv ~ 0,1 rad.

Recommended diagnostic testing of a clinical suspicion of pulmonary embolism in a pregnant patient

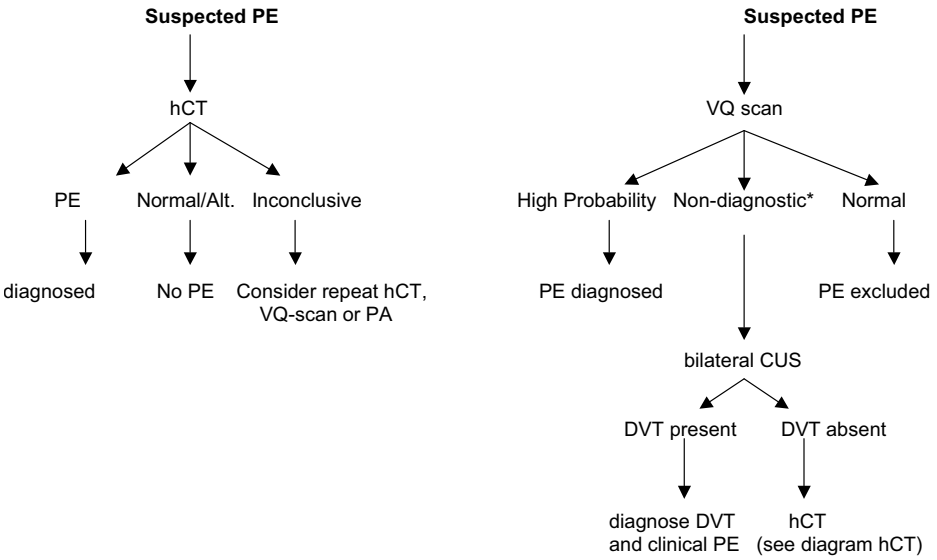
High quality evidence from prospective studies of the safety of ruling out PE by VQ scintigraphy or CT scan is lacking. Although there are no strong reasons to believe that VQ scintigraphy and CT scan results should be interpreted differently in pregnant compared to non-pregnant patients, there is a theoretical possibility of compression of the lung bases by the uterus in late pregnancy that may result in an abnormal VQ scan, the evidence of which however is lacking. Therefore, when confronted with a clinical suspicion of PE in a pregnant patient, one should start with VQ scan, a helical CT, or bilateral CUS, depending on local availability and expertise (Figure 2). Helical CT has the advantage of low fetal radiation exposure (Table 2), a low number of non-diagnostic results and the ability to make an alternative diagnosis that can explain the patient's complaints. The visualisation of an arterial filling defect is diagnostic for PE. The safety of using helical CT as a stand-alone test has been argued[18]. Two studies have shown DVT on CUS in 6 to 8% of (non-pregnant) patients with a suspicion of PE despite a negative helical CT[19;20]. These results contrast with another study in which CUS revealed DVT in only 2 of 378 (0.5%) patients with no PE on helical CT[21]. This discrepancy might be explained by the timing of CUS; in the first two studies CUS was performed before or concomitant with helical CT while in the latter study, CUS was performed after helical CT revealed no PE.

Ventilation-perfusion scintigraphy is to be considered a first line diagnostic test and rules out the diagnosis of PE when the result of the perfusion scan is normal. When a high probability scan is obtained, the diagnosis of PE can be considered confirmed. All other abnormal VQ-scan results are non-diagnostic and the diagnosis of PE needs to be confirmed or excluded by additional testing with a hCT scan or alternatively shielded pulmonary angiography. Ultrasonography can be used as a first line test to demonstrate DVT or as an additional test when VQ scanning is non-diagnostic. When CUS demonstrates DVT, further testing is not necessary and the patient can be considered to have a VTE. A normal CUS is always to be followed by additional tests to rule out PE. The roles of pre-test probability assessment and D-dimer testing in the diagnosis of suspected PE in pregnancy have yet to be defined.

Future perspectives

Although guidelines can be given for objective DVT and PE diagnosis in pregnant patients, there is a clear need for prospective studies. Two large prospective management studies in the diagnosis of pulmonary embolism in pregnancy have been started recently. In the first study in Canada a decision tree with clinical risk factors, CUS and VQ-scanning is being evaluated. In another study in the Netherlands helical CT as a first line and sole test for the diagnosis of PE is evaluated by studying the safety of withholding anticoagulants in pregnant women with clinically suspected PE and a normal CT-scan.

Figure 2
Algorithms for a clinical suspicion of PE in pregnancy



PE: Pulmonary Embolism, hCT: helical Computed Tomography, VQ scan: VentilationPerfusion scan, PA: Pulmonary Angiography, CUS: Compression UltraSonography, DVT: Deep Vein Thrombosis, *Non-diagnostic=
no high-probability and no normal result on VQ scan.

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