When should we use diagnostic imaging to investigate for pulmonary embolism in pregnant and postpartum women?

Steve Goodacre,1 Catherine Nelson-Piercy,2 Beverley Hunt,3 Wee-Shian Chan4

ABSTRACT

Pulmonary embolism (PE) is a leading cause of death in pregnancy and postpartum. Clinicians face a difficult choice when deciding whether to use diagnostic imaging to investigate for suspected PE in these patients, between risking potentially catastrophic consequences of missed diagnosis if imaging is withheld and risking unnecessary iatrogenic harm to both mother and fetus if imaging is overused. This paper explores the options for imaging and evidence for the use of clinical features, clinical predictions scores or biomarkers to select pregnant and postpartum women for imaging. It also considers where future research could be most appropriately directed.

Pulmonary embolism (PE) is a leading cause of death in pregnancy and postpartum that affects women who would otherwise expect to have a long life expectancy in full health. Furthermore, the outcome for the fetus is dependent on the outcome for the mother. Women with appropriately diagnosed and treated PE have a low risk of adverse outcome, so accurate diagnosis can result in substantial benefits. However, the investigations used to diagnose PE (imaging with VQ scanning or CT pulmonary angiography) carry risks of radiation exposure, reaction to contrast media and false positive diagnosis, are inconvenient for patients, cause unnecessary psychological distress, and incur costs for the health service. MRI has the potential to avoid radiation exposure, but evidence is currently insufficient to support inclusion in guidelines.1–3 Clinicians therefore face a difficult choice when deciding whether to use diagnostic imaging to investigate for suspected PE in pregnant and postpartum women, between risking potentially catastrophic consequences of missed diagnosis if imaging is withheld and risking iatrogenic harm if imaging is overused.

This paper explores whether diagnostic imaging should be used in all cases of suspected PE or whether clinical features, clinical predictions scores or biomarkers can be used to select women for imaging. It also considers where future research could be most appropriately directed.

CURRENT GUIDELINES AND PRACTICE

Guidelines from the Royal College of Obstetricians and Gynaecologists1 and American Thoracic Society2 recommend that pregnant or postpartum women with suspected PE should all receive diagnostic imaging, while guidelines from the European Society of Cardiology3 suggest a possible role for D-dimer in selecting patients. It is not clear how suspected PE is defined in these guidelines and the extent to which pregnant or postpartum women presenting with chest pain or shortness of breath should be selected as having suspected PE on the basis of clinical assessment. Current data show that use of a non-selective approach is resulting in a low prevalence of PE among those investigated. The most recent studies of suspected PE in pregnancy report prevalence of between 1.4 and 4.2%,4–6 while audit data from Sheffield Teaching Hospitals NHS Foundation Trust show a prevalence of 2% among those undergoing imaging. We therefore appear to be exposing around 50 women (and fetuses in pregnant women) to the risks of diagnostic imaging for each woman with PE who is able to benefit from diagnosis and treatment.

The recommendations for pregnant and postpartum women contrast with National Institute for Health and Care Excellence (NICE) guidelines for the general (non-pregnant) population with suspected PE, for whom diagnostic imaging is selectively used based upon structured clinical assessment and D-dimer measurement.6 Selective use could markedly increase the diagnostic yield of imaging. For example, non-pregnant patients with a moderate or high risk of PE, according to the Wells criteria, have PE prevalence of 16.2% and 37.5%, respectively, compared to a prevalence of 1.3% in low-risk patients.9 The diagnostic accuracy of clinical features, clinical prediction scores and D-dimer is well established in the general population with suspected PE, but is uncertain in pregnant and postpartum women. Clinical assessment or biomarkers could play an important role in selecting pregnant or postpartum women with suspected PE for imaging, but evidence from the relevant population is required.

CAN CLINICAL FEATURES, CLINICAL PREDICTION SCORES OR BIOMARKERS BE USED TO SELECT WOMEN FOR IMAGING?

To address this question, we systematically searched Medline via the PubMed interface in January 2014 for English language diagnostic studies of pregnant or postpartum women investigated for suspected PE using the search terms Pregnancy and Pulmonary Embolism [Diagnosis], Pulmonary Embolism [Radiography] or Pulmonary Embolism [Radionuclide Imaging], and contacted researchers known to the authors. We screened 198 citations and identified 11 relevant articles. These are outlined in Table 1, along with a conference abstract and paper in press identified by contact with experts.
Studies were generally retrospective, small and had low prevalence of PE, particularly in recent cohorts of unselected patients. Six of the studies focussed on the results of imaging rather than evaluating alternative diagnostic methods.\textsuperscript{5} 6 10–12 15 Those evaluating other diagnostic methods had limited power to detect an association with a reference standard diagnosis of PE. Cahill et al\textsuperscript{13} found that chest pain and low oxygen saturation were associated with a diagnosis of PE, while other features (dyspnoea, tachycardia, A–a gradient) showed no evidence of association. Deutsch et al\textsuperscript{16} also found that chest pain showed some association with a diagnosis of PE, while other features (dyspnoea, heart rate, respiratory rate (RR), blood pressure (BP) oxygen saturation, A–a gradient) did not. Bourjeily et al\textsuperscript{18} found no association between dyspnoea, chest pain, pleuritic chest pain, haemoptysis, cough, deep vein thrombosis (DVT) signs, wheeze, pleural rub, heart rate, RR or systolic BP and a diagnosis of PE.

Two studies have suggested that the modified Wells score, which was developed to diagnose PE in the non-pregnant population, may be useful in pregnant or postpartum women. O’Connor et al\textsuperscript{18} reported that a modified Wells score of six or greater (PE likely) has sensitivity of 100% and specificity of 90% for PE, while Cutts et al\textsuperscript{17} reported sensitivity of 100% (95% CI 40% to 100%) and specificity of 60% (52% to 67%). Other clinical prediction rules, such as the Geneva score\textsuperscript{19} and pulmonary embolism rule-out criteria (PERC) rule,\textsuperscript{20} have not yet been tested in pregnant or postpartum women with suspected PE.

The studies by O’Connor et al\textsuperscript{18} and Cutts et al\textsuperscript{17} ‘O’Connor and Cutts’ has been changed to ‘O’Connor et al and Cutts et al’ as per reference list. suggest a potential role for a modified Wells score in selecting women for imaging, but the main limitation is the wide CIs around estimates of sensitivity. More precise estimates of sensitivity would help to convince clinicians that a

Table 1  Diagnostic studies of pregnant or postpartum women with suspected PE

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Population, setting and duration</th>
<th>Index tests</th>
<th>Reference standard</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balan 1997\textsuperscript{10}</td>
<td>UK 82 pregnant women, one hospital, 5 years</td>
<td>None</td>
<td>VQ scan</td>
<td>31 (38%) normal</td>
</tr>
<tr>
<td>Chan 2002\textsuperscript{11}</td>
<td>Canada 113 pregnant women, 2 hospitals, 4 and 10 years</td>
<td>None</td>
<td>VQ scan</td>
<td>83 (73.5%) normal</td>
</tr>
<tr>
<td>Scansbrook 2007\textsuperscript{12}</td>
<td>UK 94 pregnant women, 1 hospital, 5 years</td>
<td>None</td>
<td>VQ scan</td>
<td>89 (92%) normal</td>
</tr>
<tr>
<td>Cahill 2009\textsuperscript{13}</td>
<td>USA 199 pregnant and 105 postpartum, 1 hospital, 5 years</td>
<td>Clinical features\textsuperscript{*}</td>
<td>108 CTPA and 196 VQ scan</td>
<td>18 (5.9%) diagnosed PE</td>
</tr>
<tr>
<td>Damodaram 2009\textsuperscript{14}</td>
<td>UK 37 pregnant women, 1 hospital, 4 years</td>
<td>D-dimer</td>
<td>VQ scan</td>
<td>13 (35%) low probability</td>
</tr>
<tr>
<td>Shahir 2010\textsuperscript{15}</td>
<td>USA 199 pregnant women, 1 hospital, 8 years</td>
<td>None</td>
<td>106 CTPA and 99 VQ scan</td>
<td>CTPA: 4/106 (3.7%) PE</td>
</tr>
<tr>
<td>Deutsch 2010\textsuperscript{16}</td>
<td>USA 102 pregnant or postpartum women, 1 hospital, 7 years</td>
<td>Clinical features\textsuperscript{†}</td>
<td>CTPA</td>
<td>VQ scans: 0 high probability, 2 intermediate, 19 low, 14 very low, 63 normal, 1 inconclusive</td>
</tr>
<tr>
<td>Hassanin 2011\textsuperscript{17}</td>
<td>Egypt 60 postpartum women, 1 hospital, years not reported</td>
<td>D-dimer</td>
<td>CTPA</td>
<td>CTPA: 13/102 (13%) PE</td>
</tr>
<tr>
<td>O’Connor 2011\textsuperscript{18}</td>
<td>Ireland 97 pregnant and 28 postpartum women, 1 hospital, 5 years</td>
<td>Modified Wells score</td>
<td>CTPA</td>
<td>CTPA: 5/103 (5%) PE</td>
</tr>
<tr>
<td>Bourjeily 2012\textsuperscript{4}</td>
<td>USA 343 pregnant women, 1 hospital, 5 years</td>
<td>Clinical features\textsuperscript{‡}</td>
<td>CTPA</td>
<td>8 (2.3%) PE</td>
</tr>
<tr>
<td>Abele 2013\textsuperscript{5}</td>
<td>Canada 74 pregnant women, 3 hospitals, 1.5 years</td>
<td>None</td>
<td>Perfusion scan and CTPA if abnormal</td>
<td>61 (82.4%) normal perfusion</td>
</tr>
<tr>
<td>Nijkeuter 2013 (abstract)\textsuperscript{7}</td>
<td>The Netherlands 149 pregnant women, 3 hospitals, 9 years</td>
<td>None</td>
<td>CTPA</td>
<td>13 (17.6%) abnormal—1 (1.4%) PE on CTPA</td>
</tr>
<tr>
<td>Cutts 2014\textsuperscript{7}</td>
<td>UK and Australia 183 pregnant women, 2 hospitals, 4 years</td>
<td>Modified Wells score</td>
<td>VQ scan</td>
<td>4 (2%) high probability</td>
</tr>
</tbody>
</table>

\*Chest pain, dyspnoea, heart rate, oxygen saturation, A–a gradient.\textsuperscript{†}Chest pain, dyspnoea, heart rate, RR, BP, oxygen saturation, A–a gradient.\textsuperscript{‡}Chest pain, dyspnoea, pleuritic chest pain, haemoptysis, cough, DVT signs, wheeze, pleural rub, heart rate, RR, systolic BP. CTPA, CT pulmonary angiography; PE, pulmonary embolism.
clinical prediction score can reliably identify a low-risk group. Furthermore, for Wells criteria to be of value in pregnant or postpartum women, the criterion asking whether any other diagnosis is more likely than PE needs to be answered appropriately. Caution may lead a clinician to answer ‘no’, whereas the low prevalence of PE suggests that another diagnosis must be more likely in most cases.

Studies of D-dimer in pregnant and postpartum women suggest that high levels of positivity at conventional thresholds limit the diagnostic value of this test. However, indirect evidence from studies of D-dimer for suspected DVT in pregnancy suggests potential diagnostic value. Chan et al reported 100% sensitivity (95% CI 77% to 100%) and 60% specificity (52% to 68%) for the qualitative SimpliRED D-dimer in suspected DVT. Another study of five commercially available assays reported specificities ranging from 6% to 23%, but further analysis suggested that using a higher threshold for positivity could improve specificity without compromising sensitivity. It is possible that a pregnancy-specific threshold of, for example, double the conventional threshold could improve specificity without undermining sensitivity, but this hypothesis needs to be tested.

A number of studies have compared pregnant or postpartum women with PE to an asymptomatic control group. These studies aim to identify risk factors for developing PE in pregnancy rather than evaluate diagnostic accuracy, but they may identify variables that could be diagnostically useful. The findings are summarised in Table 2. Knight et al compared women with antenatal PE identified through the UKOSS (UK Obstetric Surveillance System) research platform to pregnant controls, and showed that multiparity and Body Mass Index (BMI) were independent predictors of developing PE. Kane et al used cases identified by the Scottish Morbidity Record 2 (SMR2) to show that women aged over 35 years, with previous venous thromboembolism (VTE), pre-eclampsia, antenatal haemorrhage or postnatal haemorrhage, were more likely to develop PE than those without these characteristics. Henriksson et al showed that VTE is associated with pregnancy following in vitro fertilisation. Sultan et al linked primary (Clinical Practice Research Datalink) and secondary (Hospital Episode Statistics) care records to show that BMI, complications of pregnancy (pre-eclampsia, antenatal or postnatal haemorrhage, diabetes, hyperemesis), comorbidities (varicose veins, cardiac disease, hypertension) and recent hospital admission were associated with an increased risk of developing PE.

**WHAT FURTHER RESEARCH IS NEEDED?**

The main barrier to implementation of any strategy to identify women who can forego diagnostic imaging is imprecision in the estimate of sensitivity. Pregnant and postpartum women with suspected PE have a very low prevalence of PE. This means that even a large cohort study will have few women with confirmed PE, so any estimate of sensitivity will be imprecise and have a wide CI. For example, a cohort study of 500 women will identify 10 with PE (assuming 2% prevalence) giving a 95% CI of 66% to 100% for a test with 100% sensitivity. If we want to identify a test with 100% sensitivity and a lower 95% CI exceeding 90% we will need a cohort of 2000 patients.

Data from UKOSS suggest an incidence of 1.3 per 10 000 maternities for antenatal PE, while data from the Scottish Morbidity Record (SMR2) suggest a combined incidence of 2.0 per 10 000 maternities for antenatal and postnatal PE. With 723 913 live births in England and Wales in 2011, these data suggest 94 cases of antenatal PE or 145 cases of antenatal or postnatal PE per year. Thus, a typical hospital would only see one case of PE in pregnant or postpartum women per year. Recent studies identified in our literature review confirm a rate of one or two cases per hospital per year. An appropriately powered cohort study will therefore require multicentre and probably multinational enrolment, a high recruitment rate, substantial funding and many years to complete. A case control design can provide an alternative method when disease prevalence is low, but this design may be associated with a substantial risk of bias and lead to overestimation of accuracy compared to a cohort study. This bias could be reduced by ensuring that cases and controls are representative samples rather than being severe cases and healthy population controls, but uncertainty about potential bias would remain.

**HOW SHOULD WE MANAGE PATIENTS IN THE MEANTIME?**

Further research is likely to be challenging, and in the meantime decisions have to be made on the basis of existing evidence. In the absence of high-quality data, it is tempting to take a cautious approach and use diagnostic imaging in all cases, but this approach protects the clinician rather than the patient. The risks of radiation exposure are well recognised, and guidelines suggest that women should be advised of the risks of childhood cancer associated with VQ scanning and CT pulmonary angiography (CTPA) (1 in 280 000 and 1 in 1 000 000, respectively), and the increased lifetime risk of maternal breast cancer associated with CTPA (up to 13.6% against a background risk of 1 in 200). Radiation-induced malignancy may arise many years after investigation allowing the link to exposure to go unrecognised in individual cases, and the clinician to escape blame. The risks of overdiagnosis are often overlooked. CTPA has been estimated to have sensitivity and specificity of 80–100% and 78–100%, respectively (NICE). The evidence for VQ scanning is more limited and provides estimates of 41–100% for sensitivity and 72–97% for specificity. If a test with 90% sensitivity and 90% specificity is applied to a patient with a 2% pretest probability of disease, then Bayesian analysis suggests that the post-test probability of disease in a patient with a positive test will be around 15%. So if CTPA or VQ scanning is used to diagnose PE in a low-risk population, then it seems that most of the women who are diagnosed and treated will not actually have PE. As with radiation-induced malignancy, clinicians who overdiagnose PE are likely to be unaware of the harm they are causing.

These observations suggest that a cautious approach with recourse to radiological investigation for all cases may actually harm women. To explore this further, a formal decision analysis could be used to weigh up the risks and benefits of investigation for PE and identify a threshold pretest probability below which
the risks of investigation outweigh the benefits. This would be a complex analysis involving synthesis of varied data sources and would be limited by uncertainty around key parameters, especially our estimate of the benefit of treating PE. However, it would be a logical first step in formalising the decision problem, which could be used to guide future research and might produce some surprising findings.

In the meantime, we should recognise that uncertainty in our ability to identify women with a low clinical probability of PE does not justify unselective use of imaging, and limitations in previous studies do not justify rejecting the available data. The existing evidence may not be perfect but it can assist us in identifying women who are at risk of PE. Guidelines may suggest that all women with suspected PE should receive imaging, but the presence of chest pain or shortness of breath on their own do not necessarily suggest a suspicion of PE. We suggest a detailed history and examination are taken from the patient, carefully reviewing their symptomatology and their past history. Women with none of the potential clinical predictors identified above are very unlikely to have PE, and are potentially more likely to be harmed by investigation than receive benefit. Future research into clinical predictors and biomarkers is likely to be limited by imprecision or risk of bias, but it can still provide worthwhile new knowledge.

Finally, two additional issues need to be taken into account in determining clinical practice and future research. First, it is not clear whether diagnostic strategies should be the same for pregnant and postpartum women. The existing data are insufficient to distinguish between these groups, but there are good theoretical reasons to assume that clinical characteristics and diagnostic tests may perform differently in pregnant and postpartum women, and that the risks and benefits of imaging (most obviously to the fetus or baby) will differ between pregnant and postpartum women. Second, the risks and benefits of imaging will depend upon the imaging strategy used. Comparison of CTPA to VQ scanning is beyond the scope of this paper, but studies in pregnant patients suggest that they are not equivalent. CTPA has better interobserver agreement, but is limited by a higher rate of non-diagnostic studies. Any difference in diagnostic accuracy will translate into a difference in the risk of missed diagnosis and associated harm. As described above, the risk of childhood cancer is greater for VQ scanning than CTPA, but the risk of maternal breast cancer is increased with CTPA. Considering these issues together it might be appropriate to use different imaging strategies in pregnant and postpartum women. In general, the difficult judgment of whether the benefits of investigation outweigh the risks needs to take individual patient characteristics and preferences into account.

CONCLUSION

Recent studies suggest that pregnant and postpartum women undergoing diagnostic imaging have a very low risk of PE, such that the harms of investigation with diagnostic imaging may outweigh the benefits. Clinical predictors such as multiparity, BMI, complications of pregnancy, previous VTE, peripheral oxygen saturation and modified Wells score may be used to identify women at higher risk of PE who could be selected for imaging. Formal decision analysis of the risks and benefits of diagnostic imaging would be helpful, but women without these clinical predictors seem unlikely to benefit from imaging. Research is required to improve our knowledge of the value of clinical predictors and explore the use of D-dimer at a pregnancy-specific threshold. However, the low prevalence of PE means that definitive cohort studies to estimate diagnostic accuracy may not be feasible, whereas a case-control design offers a more efficient way of estimating sensitivity with acceptable precision.

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