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

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The clinical problem

Pulmonary embolism (PE) is a leading cause of death in pregnancy and postpartum that affects women who would otherwise expect to have 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. Magnetic resonance imaging 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 over-used.

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 Gynaecologists [1] and American Thoracic Society [2] recommend that pregnant or postpartum women with suspected PE should all receive diagnostic imaging, while guidelines from the European Society of Cardiology [3] 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%, [4-7] 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 every one 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. [8] 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.

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

First author and year	Country	Population, setting & duration	Index tests	Reference standard	Main findings
Balan 1997 [10]	UK	82 pregnant women, one hospital, 5 years	None	VQ scan	31 (38%) normal 19 (23%) low probability 14 (17%) intermediate 18 (22%) high
Chan 2002 [11]	Canada	113 pregnant women, 2 hospitals, 4 & 10 years	None	VQ scan	83 (73.5%) normal 28 (24.8%) nondiagnostic 2 (1.8%) high probability
Scarsbrook 2007 [12]	UK	94 pregnant women, 1 hospital, 5 years	None	VQ scan	89 (92%) normal 7 (7%) nondiagnostic 1 (1%) high probability
Cahill 2009 [13]	USA	199 pregnant and 105 postpartum, 1 hospital, 5 years	Clinical features[1]	108 CTPA & 196 VQ scan	18 (5.9%) diagnosed PE Low oxygen saturation and chest pain predicted PE, other features did not

Damodram 2009 [14]	UK	37 pregnant women, 1 hospital, 4 years	D-dimer	VQ scan	13 (35%) low probability 24 (65%) intermediate or high probability D-dimer sensitivity 73%, specificity 15%
Shahir 2010 [15]	USA	199 pregnant women, 1 hospital, 8 years	None	106 CTPA & 99 VQ scan	CTPA: 4/106 (3.7%) PE VQ scans: 0 high probability, 2 intermediate, 19 low, 14 very low, 63 normal, 1 inconclusive
Deutsch 2010 [16]	USA	102 pregnant or postpartum women, 1 hospital, 7 years	Clinical features[2]	CTPA	CTPA: 13/102 (13%) PE Only chest pain predicted PE
Hassanin 2011 [17]	Egypt	60 postpartum women, 1 hospital, years not reported	D-dimer	CTPA	4 (6.6%) PE D-dimer positive in all cases
O'Connor 2011 [18]	Ireland	97 pregnant and 28 postpartum women, 1 hospital, 5 years	Modified Wells score D-dimer Blood gas ECG	CTPA	CTPA: 5/103 (5%) PE Modified Wells 100% sensitive & 90% specific D-dimer 0% sensitive and 74% specific

Bourjeilly 2012 [4]	USA	343 pregnant women, 1 hospital, 5 years	Clinical features[3]	CTPA	8 (2.3%) PE No association found between clinical features and PE
Abele 2013 [5]	Canada	74 pregnant women, 3 hospitals, 1.5 years	None	Perfusion scan & CTPA if abnormal	61 (82.4%) normal perfusion 13 (17.6%) abnormal – 1 (1.4%) PE on CTPA
Nijkeuter 2013 (abstract) [6]	Netherlands	149 pregnant women, 3 hospitals, 9 years	None	CTPA	6 (4.2%) PE 8 (5.6%) inconclusive 129 (90.2%) normal
Cutts 2014 [7]	UK & Australia	183 pregnant women, 2 hospitals, 4 years	Modified Wells score	VQ scan	4 (2%) high probability 6 (3%) nondiagnostic 173 (95%) normal D-dimer positive in 48/51 Modified Wells score predicted PE

[1]Chest pain, dyspnea, heart rate, oxygen saturation, A-a gradient

[2]Chest pain, dyspnea, heart rate, respiratory rate, blood pressure, oxygen saturation, A-a gradient

[3]Chest pain, dyspnea, pleuritic chest pain, haemoptysis, cough, DVT signs, wheeze, pleural rub, heart rate, respiratory rate, systolic blood pressure

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. [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 [13] found that chest pain and low oxygen saturation were associated with a diagnosis of PE, but other features (dyspnoea, tachycardia, A-a gradient) showed no evidence of association. Deutsch et al [16] also found that chest pain showed some association with a diagnosis of PE, while other features (dyspnoea, heart rate, respiratory rate, blood pressure, oxygen saturation, A-a gradient) did not. Bourjeily et al [4] found no association between dyspnoea, chest pain, pleuritic chest pain, haemoptysis, cough, DVT signs, wheeze, pleural rub, heart rate, respiratory rate or systolic blood pressure 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 [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 [7] reported sensitivity of 100% (95% confidence interval 40 to 100%) and specificity of 60% (52 to 67%). Other clinical prediction rules, such as the Geneva score [19] and PERC rule, [20] have not yet been tested in pregnant or postpartum women with suspected PE.

The studies by O'Connor [18] and Cutts [7] suggest a potential role for a modified Wells score in selecting women for imaging but the main limitation is the wide confidence intervals around estimates of sensitivity. More precise estimates of sensitivity would help to convince clinicians that a 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 [7,14,17,18] 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 [21] reported 100% sensitivity (95% confidence interval 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 [22] reported specificities ranging from 6 to 23% but further analysis suggested that using a higher threshold for positivity could improve sensitivity without compromising specificity. 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 [23] compared women with antenatal PE identified through the UKOSS (United Kingdom 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 [24] used cases identified by the Scottish Morbidity Record 2 (SMR2) to show that women aged over 35, 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 [25] showed that VTE is associated with pregnancy following in vitro fertilisation. Sultan et al [26] 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), co-morbidities (varicose veins, cardiac disease, hypertension) and recent hospital admission were associated with an increased risk of developing PE.

Table 2: Risk factors for PE in pregnancy

Pre-existing	**Pregnancy-related**
Age over 35	Multiparity
Body Mass Index	In vitro fertilisation
Previous venous thromboembolism	Pre-eclampsia
Varicose veins	Antenatal or postnatal haemorrhage
Cardiac disease	Gestational diabetes
Hypertension	Hyperemesis
Recent hospital admission	

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 confidence interval. For example, a cohort study of 500 women will identify 10 with PE (assuming 2% prevalence) giving a 95% confidence interval of 66 to 100% for a test with 100% sensitivity. If we want to identify a test with 100% sensitivity and a lower 95% confidence interval exceeding 90% we will need a cohort of 2000 patients.

Data from UKOSS [23] suggest an incidence of 1.3 per 10,000 maternities for antenatal pulmonary embolism (PE), while data from the Scottish Morbidity Record (SMR2) [24] 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 [4-7,15,16,18]. 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 [27] 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 [1] suggest that women should be advised of the risks of childhood cancer associated with VQ scanning and 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 over-diagnosis 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. [8] If a test with 90% sensitivity and 90% specificity is applied to a patient with a 2% pre-test 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 over-diagnose 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 pre-test 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, 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 inter-observer agreement [28] but is limited by a higher rate of non-diagnostic studies [29]. Any difference in diagnostic accuracy will translate into a difference in the risk of misdiagnosis 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.

Contributorship

SG conceived the idea for the paper and wrote the first draft. All authors contributed to redrafting and approved the final draft.

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Conflicts of interest

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