Selecting pregnant or postpartum women with suspected pulmonary embolism for diagnostic imaging: the DiPEP diagnostic study with decision-analysis modelling

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Scientific summary

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Background

Pulmonary embolism (PE) is a leading cause of death in pregnancy and post partum. Symptoms suggesting PE are very common in pregnancy and post partum. As a consequence, many pregnant and postpartum women undergo radiological investigation for a suspected PE with a low yield of positive diagnosis. Clinical decision rules use features of the patient history and examination in a structured manner to estimate the probability of disease. A number of biomarkers are known to be increased in the presence of PE. Clinical decision rules or biomarkers could be used to select women with suspected PE for radiological investigation or discharge without imaging.

Objectives

We aimed to estimate the diagnostic accuracy, effectiveness and cost-effectiveness of strategies (including clinical decision rules) for selecting pregnant or postpartum women with a suspected PE for imaging, and determine the feasibility and value of information of further prospective research.

Our specific objectives were to:

- use expert consensus to derive three new clinical decision rules (with different trade-offs between sensitivity and specificity) for pregnant and postpartum women with a suspected PE
- estimate the diagnostic accuracy of clinical variables, our expert-derived clinical decision rules, existing clinical decision rules [Wells's PE criteria, Geneva score and a PE rule-out criteria (PERC)] and the D-dimer measurement in pregnant and postpartum women with suspected PE
- use a statistical analysis of women with a diagnosed or suspected PE to derive a new clinical decision rule for pregnant and postpartum women with suspected PE
- explore the potential diagnostic value of biomarkers for PE in pregnant and postpartum women
- determine the feasibility of using a prospective cohort design to validate a new clinical decision rule or biomarker
- estimate the effectiveness of different strategies, in terms of adverse outcomes from venous thromboembolism (VTE), bleeding and radiation exposure, and cost-effectiveness, measured as the incremental cost per quality-adjusted life-year (QALY)
- estimate the value of information associated with further research.

Methods

The study involved (1) an expert consensus study to develop three new clinical decision rules; (2) a case–control study of women with a diagnosed PE identified through the UK Obstetric Surveillance System (UKOSS) research platform and women with a suspected PE recruited from emergency departments and maternity units at 11 prospectively recruiting sites; (3) a biomarker study involving the prospectively recruited women and additional women with diagnosed deep-vein thrombosis (DVT); and (4) decision-analysis modelling of effectiveness, cost-effectiveness and value of information.

The study population included (1) any pregnant or postpartum women with a diagnosed PE who had presented with suspected PE to a hospital reporting to the UKOSS research platform; (2) pregnant and postpartum women presenting with suspected PE to 11 prospectively recruiting sites; and (3) women with DVT diagnosed at the prospectively recruiting sites. We excluded women who required resuscitation at

presentation from all groups and those who were unable to consent or who had an existing diagnosis of PE from the prospectively recruited group.

The nominated clinician for UKOSS and the research nurse/midwife at prospectively recruiting sites collected data detailing potential clinical predictors, blood tests results, diagnostic imaging, treatment and adverse events. Research nurses/midwives also collected a blood sample from women with suspected PE or diagnosed DVT at the prospectively recruiting sites, and reviewed hospital records at 30 days. Prospectively recruited women were then sent a questionnaire to record adverse events, health-care use and health utility. Two independent assessors, blind to clinical predictors and blood results, classified participants as having PE using diagnostic imaging results and details of treatments and adverse events. The primary analysis was limited to women with PE diagnosed by imaging or post-mortem examination, and women with PE ruled out after imaging. Secondary analyses explored the impact of including women with clinically diagnosed PE or PE ruled out without imaging, and the impact of excluding subsegmental PE.

Blood samples were centrifuged, stored and then transported to Guy's and St Thomas' NHS Foundation Trust for analysis using the following assays: D-dimer [enzyme-linked immunosorbent assay (ELISA)], D-dimer [Innovance (Siemens Healthcare Diagnostics Products GmbH, distributed by Sysmex UK Ltd, Milton Keynes, UK)], plasmin–antiplasmin, prothrombin fragment 1 + 2 (PF 1 + 2), thrombin generation, prothrombin time, activated partial thromboplastin time (APTT), Clauss fibrinogen, soluble tissue factor, troponin I, B-type natriuretic peptide (BNP), C-reactive protein (CRP) and mid-regional pro-atrial natriuretic peptide (MRproANP).

The sample size was ultimately determined by the incidence of a diagnosed and suspected PE, but we estimated that over 18 months we would identify 150 women with a diagnosed PE and 250 women with a suspected PE, resulting in around 155 patients and 245 controls. This would allow the estimation of sensitivity or specificity of 90% with standard errors (SEs) of around 2.5% and 2.0%, respectively. We increased the planned sample size after starting recruitment to ensure that adequate numbers would be included in the primary analysis.

Logistic regression was used to identify associations between clinical predictors and a PE diagnosis. The diagnostic performance of existing clinical decision rules (Wells's PE criteria, simplified revised Geneva score and PERC rule) and those developed by expert consensus was assessed by constructing receiver operating characteristic (ROC) curves, calculating the area under the curve (AUC) and calculating the sensitivity and specificity at key decision-making thresholds. The diagnostic performance of biomarkers was assessed by comparing distributions in women with and without PE, constructing ROC curves, calculating the AUC and calculating sensitivity and specificity at a predefined threshold based on the 99th percentile for a normal population.

Decision-analysis modelling was used to estimate the costs incurred and the expected outcomes from thromboembolism, bleeding and radiation exposure if a hypothetical cohort of pregnant or postpartum women based on the study population was investigated for suspected PE using different strategies, including no imaging, selective imaging and imaging for all. Outcomes were modelled to estimate the QALYs accrued by each strategy and the incremental cost per QALY gained by each strategy compared with the next most effective alternative.

Results

The expert consensus study derived three clinical decision rules for use in pregnant and postpartum women with a suspected PE: a primary rule that provided an optimal balance of sensitivity and specificity, a sensitive rule that maximised sensitivity at the expense of specificity and a specific rule that maximised specificity at the expense of sensitivity.

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We identified 198 women with a diagnosed PE who met our inclusion criteria, of whom 163 had a PE confirmed by imaging or post-mortem examination and were included in the primary analysis. We identified 324 women with suspected PE, of whom 18 had PE confirmed by imaging and 259 had PE ruled out after imaging. The primary analysis therefore involved 181 women with PE and 259 women without PE.

Univariable logistic regression showed that the number of previous pregnancies beyond 24 weeks' gestation ($p = 0.017$), surgery (including caesarean section) in the previous 4 weeks ($p = 0.001$), no history of varicose veins ($p = 0.045$), no long-haul travel during pregnancy ($p = 0.006$), receiving thromboprophylaxis ($p < 0.001$), higher temperature ($p = 0.003$), lower oxygen saturation ($p < 0.001$), overall diagnostic impression, suggesting PE using a strict interpretation ($p < 0.001$), PE-related chest radiograph abnormality ($p = 0.01$) and non-PE-related chest radiograph abnormality ($p = 0.001$) were associated with PE. All other clinical features showed no significant association with PE.

The AUC and sensitivity and specificity at the usual recommended threshold for the clinical decision rules were 0.626, 60.9% and 58.5% for the primary consensus rule; 0.620, 95.9% and 3.5% for the sensitive consensus rule; 0.589, 36.1% and 78.3% for the specific consensus rule; 0.621, 67.5% and 51.9% for the PERC score; 0.579, 44.4% and 63.6% for the simplified Geneva score; 0.577, 49.0% and 61.7% for Wells's PE criteria using a permissive interpretation of diagnostic impression; and 0.732, 37.6% and 89.5% for Wells's PE criteria using a strict interpretation of diagnostic impression.

D-dimer measurements were recorded as part of routine care for 44 out of 198 (22%) women with a diagnosed PE and 156 out of 324 (48%) women with a suspected PE. The primary analysis, using results from 43 women with PE and 125 without PE, showed that sensitivity and specificity were 88.4% [95% confidence interval (CI) 74.1% to 95.6%] and 8.8% (95% CI 4.7% to 15.6%) using the hospital laboratory threshold, and 69.8% (95% CI 53.7% to 82.3%) and 32.8% (95% CI 24.8% to 41.9%) using predefined gestation-specific thresholds.

Multivariable analysis showed that the most accurate model used previous VTE, long-haul travel during pregnancy, multiple pregnancy, oxygen saturation (as a continuous variable), surgery in the previous 4 weeks, temperature (as a continuous variable) and PE-related chest radiograph abnormality to predict PE with an AUC of 0.724 (95% CI 0.669 to 0.779). The ROC curve shows that specificity would have to be as low as 20% to achieve a level of sensitivity (> 95%) that was acceptable to allow imaging to be avoided. We therefore did not proceed to internal validation or attempt to make the model more clinically credible or usable.

The optimal model developed by recursive partitioning used body mass index (BMI), trimester, oxygen saturation and heart rate. The AUC was 0.657 (95% CI 0.611 to 0.703) and the threshold that provided a level of sensitivity of > 95% had a corresponding specificity of 5%.

Usable blood samples were taken from 18 women with diagnosed DVT and 310 women with suspected PE, of whom 18 had PE confirmed by imaging and 247 had PE ruled out after imaging and were included in the primary analysis. Mean biomarker levels significantly differed between women with and without PE only for Clauss fibrinogen ($p = 0.007$), ELISA D-dimer ($p = 0.001$), Innovance D-dimer ($p = 0.004$), thrombin generation lag time ($p < 0.001$), thrombin generation time to peak ($p = 0.001$) and plasmin antiplasmin ($p = 0.004$). The AUC for each biomarker was as follows: 0.669 (95% CI 0.570 to 0.768) for APTT, 0.549 (95% CI 0.453 to 0.645) for BNP, 0.542 (95% CI 0.445 to 0.639) for CRP, 0.589 (95% CI 0.476 to 0.701) for Clauss fibrinogen, 0.668 (95% CI 0.561 to 0.776) for the ELISA D-dimer, 0.651 (95% CI 0.545 to 0.758) for the Innovance D-dimer, 0.524 (95% CI 0.418 to 0.630) for MRproANP, 0.562 (95% CI 0.462 to 0.661) for PF 1 + 2, 0.639 (95% CI 0.536 to 0.742) for plasmin–antiplasmin, 0.613 (95% CI 0.508 to 0.718) for prothombin time, 0.702 (95% CI 0.598 to 0.806) for thrombin generation lag time, 0.559 (95% CI 0.437 to 0.681) for thrombin generation endogenous potential, 0.596 (95% CI 0.478 to 0.715) for thrombin generation peak, 0.655 (95% CI 0.541 to 0.769) for thrombin generation time to peak, 0.531 (95% CI 0.424 to 0.638) for tissue factor and 0.597 (95% CI 0.499 to 0.695) for troponin. The ROC curve analysis showed that only

thrombin generation lag time had any potential to rule out PE with sufficient sensitivity while achieving meaningful specificity, with a sensitivity of 97% and a specificity of 25% at the threshold that optimised sensitivity. The repeat analysis excluding women who had received anticoagulation was limited by the small number of women who had PE ($n = 4$).

The study recruited women with suspected PE (prevalence of 7.1%) at a rate of 1.7 women per site per month. This suggests that a prospective cohort study would require 50 sites to recruit for 2 years to achieve a sample size of 2040, including 145 women with PE, which would be sufficient to estimate the sensitivity with acceptable precision.

The health economic analysis showed that a strategy of scanning all women with suspected PE accrued more QALYs and incurred fewer costs than any selective strategy based on a clinical decision rule, and was therefore the dominant strategy. This finding was robust in the sensitivity analysis and the scenario analysis exploring assumptions in the model. A threshold analysis showed that a clinical decision rule to select women for imaging would need to have a sensitivity exceeding 97.5% to be cost-effective compared with the non-selective use of scanning. The value-of-information analysis showed that the value of conducting further research into parameters used in the economic model was likely to be below the cost of conducting further research into any subset of feasible parameters.

Conclusions

We were unable to identify any clinical decision rule or biomarker that could be used to rule out PE in pregnant and postpartum women with acceptable sensitivity while achieving worthwhile specificity. Decision-analysis modelling showed that a strategy of non-selective scanning for all women dominated selective strategies based on decision rules. We found that many clinical features thought to be diagnostically useful for PE showed either no association or a counter-intuitive association with the absence of PE. This may be explained by the selection of women for investigation in secondary care. Those with risk factors for PE or clinical features suggesting PE may be more likely to be referred or to self-present for investigation. The prevalence of PE in those with suspected PE (7.1% overall and 6.5% in the primary analysis population) was higher than suggested by previous data, indicating that, potentially, the NHS is already selecting an appropriate population for hospital investigation.

The accuracy of the biomarkers is likely to have been undermined by the receipt of anticoagulation prior to sampling, but the removal of samples from women who had received anticoagulation left too few women with PE for a meaningful analysis. This highlights a significant practical problem in testing and using biomarkers when guidelines recommend thromboprophylaxis for many women and early use of anticoagulation if PE is suspected.

Our findings do not support the use of clinical decision rules and biomarkers (including D-dimer) in selecting women with suspected PE for imaging. We cannot conclude that all women should receive imaging, as a proportion of the study cohort with suspected PE did not receive imaging and we found no evidence of missed PE. However, a low threshold for scanning is likely to be appropriate given the costs and risks of misdiagnosis highlighted in the decision-analysis modelling.

We have shown that a prospective cohort study to derive or validate a clinical decision rule or biomarker would be feasible, albeit would require a large number of sites (more than one-quarter of all maternity units in the UK) and substantial resources. However, the accuracy of decision rules and biomarkers reported in our study is insufficient to justify a large prospective cohort study to derive a new decision rule or test existing decision rules or biomarkers. Future research efforts would be better directed at developing new biomarkers or alternative diagnostic techniques.

The current Royal College of Obstetricians and Gynaecologists guidance suggests that women should be given information about the risks and benefits of investigation and involved in decision-making. Our

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decision-analysis model has identified data sources and methods for weighing the relative risks and benefits of imaging, but has also highlighted the complexity of decision-making. Future research could be used to develop better ways of presenting information regarding the relative risks and benefits of investigation for suspected PE in pregnancy and post partum.

Trial registration

This trial is registered as ISRCTN21245595.

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