
Article:
Goodacre, S. orcid.org/0000-0003-0803-8444, Horspool, K., Nelson-Piercy, C. et al. (7 more authors) (2019) The DiPEP (Diagnosis of PE in Pregnancy) study: An observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum. BJOG: An International Journal of Obstetrics and Gynaecology, 126 (3). pp. 383-392. ISSN 1470-0328

https://doi.org/10.1111/1471-0528.15286

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DOI: 10.1111/1471-0528.15286
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Maternal medicine

The DiPEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum

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Accepted 24 April 2018. Published Online 15 June 2018.

Objective To identify clinical features associated with pulmonary embolism (PE) diagnosis and determine the accuracy of decision rules and D-dimer for diagnosing suspected PE in pregnant/postpartum women

Design Observational cohort study augmented with additional cases.

Setting Emergency departments and maternity units at eleven prospectively recruiting sites and maternity units in the United Kingdom Obstetric Surveillance System (UKOSS)

Population 324 pregnant/postpartum women with suspected PE and 198 pregnant/postpartum women with diagnosed PE

Methods We recorded clinical features, elements of clinical decision rules, D-dimer measurements, imaging results, treatments and adverse outcomes up to 30 days

Main outcome measures Women were classified as having PE on the basis of imaging, treatment and adverse outcomes by assessors blind to clinical features and D-dimer. Primary analysis was limited to women with conclusive imaging to avoid work-up bias. Secondary analyses included women with clinically diagnosed or ruled out PE.

Results The only clinical features associated with PE on multivariate analysis were age (odds ratio 1.06; 95% confidence interval 1.01–1.11), previous thrombosis (3.07; 1.05–8.99), family history of thrombosis (0.35; 0.14–0.90), temperature (2.22; 1.26–3.91), systolic blood pressure (0.96; 0.93–0.99), oxygen saturation (0.87; 0.78–0.97) and PE-related chest x-ray abnormality (13.4; 1.39–130.2). Clinical decision rules had areas under the receiver-operator characteristic curve ranging from 0.577 to 0.732 and no clinically useful threshold for decision-making. Sensitivities and specificities of D-dimer were 88.4% and 8.8% using a standard threshold and 69.8% and 32.8% using a pregnancy-specific threshold.

Conclusions Clinical decision rules and D-dimer should not be used to select pregnant or postpartum women with suspected PE for further investigation. Clinical features and chest x-ray appearances may have counter-intuitive associations with PE in this context.

Keywords Clinical decision rule, D-dimer, postpartum, pregnancy, pulmonary embolism.

Tweetable abstract Clinical decision rules and D-dimer are not helpful for diagnosing pregnant/postpartum women with suspected PE

Linked article This article is commented on by F Okonofua, p. 393 in this issue.To view this mini commentary visit https://doi.org/10.1111/1471-0528.15309.

Please cite this paper as: Goodacre S, Horspool K, Nelson-Piercy C, Knight M, Shephard N, Lecky F, Thomas S, Hunt BJ, Fuller G on behalf of the DiPEP research group. The DiPEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest x-ray for suspected pulmonary embolism in pregnancy and postpartum. BJOG 2019;126:383–392.

Study registration

ISRCTN registry ISRCTN21245595 (http://www.isrctn.com/ISRCTN21245595)

Introduction

Pulmonary embolism (PE) is the leading direct cause of death in pregnancy and postpartum.[1] Symptoms suggesting PE are common in pregnancy and postpartum. Suspected PE is therefore a common presentation to emergency departments and maternity units by pregnant and postpartum women. Recent studies[2] have reported a low positive yield from investigation so many women are undergoing negative imaging involving potentially harmful radiation. Guidelines from the American Thoracic Society[3] and Royal College of Obstetricians and Gynaecologists[4] recommend that all pregnant and postpartum women with suspected PE should receive diagnostic imaging, whereas guidelines from the European Society of Cardiology[5] suggest a possible role for D-dimer in selecting patients.

Clinical decision rules use features of the patient history and examination to estimate the probability of PE in people with suspected PE.[6–8] Plasma D-dimers are specific cross-linked fibrin derivatives produced when fibrin is degraded by plasmin, elevated levels indicating thrombolysis. They are elevated in venous thromboembolism (VTE) but also in other conditions such as pregnancy, pre-eclampsia, infections, malignancy and postoperative states. Clinical decision rules and D-dimer have been shown to accurately identify low risk patients in the non-pregnant population with suspected PE who can be discharged without diagnostic imaging, and guidelines now recommend this practice.[5,9]

A recent review[2] found insufficient data to support a similar role for clinical decision rules and D-dimer in pregnant and postpartum women. The main limitation was the low prevalence of PE in cohorts with suspected PE and consequent lack of precision in estimates of diagnostic sensitivity. Low prevalence means that the ideal study design to estimate diagnostic accuracy, a cohort study, would provide an imprecise estimate of sensitivity unless it was extremely large. A case-control study could provide a more precise estimate, albeit with a higher risk of bias.[10] A compromise between these designs is a cohort study augmented with additional cases of confirmed disease to increase the precision of estimates of sensitivity.

We undertook a prospective cohort study augmented with additional retrospective cases to determine whether clinical features, individually or in the form of a clinical decision rule, or D-dimer could be used to select pregnant and postpartum women for diagnostic imaging.

Methods

Study population

We identified participants from two sources over the same time period: (1) Emergency departments and maternity units at eleven prospectively recruiting sites identified women presenting with suspected PE during pregnancy or postpartum; (2) The United Kingdom (UK) Obstetric Surveillance System (UKOSS) research platform was used to retrospectively identify women across all UK hospitals who received a diagnosis of PE during pregnancy or postpartum (up to 42 days). We excluded women who presented needing life support on arrival at hospital from both groups; women whose PE was identified as an incidental finding from the diagnosed PE group; and women who had been diagnosed with PE in the current pregnancy before the start of the study, were unable or unwilling to provide informed consent, aged <16 years or previously recruited to the study from the suspected PE group.

The diagnosed PE group were identified as (1) PE confirmed using imaging (angiography, CT, magnetic resonance imaging or ventilation–perfusion scan showing a high probability of PE), (2) PE confirmed at surgery or post-mortem, or (3) Clinical diagnosis of PE resulting in a course of anticoagulation therapy for more than one week, although the third group was only included in secondary analysis. The suspected PE group were identified if a clinician determined that investigation for PE would be required. This resulted in most cases receiving diagnostic imaging but a proportion did not, either due to a more senior clinician deciding that imaging was not indicated or the woman declining imaging. Furthermore a proportion of women in both groups had equivocal imaging results. Thus both the diagnosed PE and suspected PE groups included a proportion of women in whom PE was clinically diagnosed or ruled out (i.e. without definitive imaging, surgery or post-mortem). We planned *a priori* that primary analysis would be limited to women with imaging, surgery or post-mortem confirmation or rule-out of PE with secondary analyses exploring the inclusion of women with clinically diagnosed or ruled out PE. Our rationale was that clinical diagnosis could be based on the index tests we were planning to evaluate and would thus be prone to bias.

Sampling

Suspected PE: Clinicians in the participating hospitals prospectively identified pregnant or postpartum woman with suspected PE considered to require diagnostic imaging. They contacted the research nurse or recruiting clinician, who provided women with study information and checked eligibility criteria. Informed consent to participate was then sought.

Diagnosed PE: Nominated clinicians in each consultant-led maternity unit in the UK were sent a card each month and asked to report all cases of antenatal or postnatal PE. In addition, ascertainment of any maternal deaths from PE occurring during the study period was checked through MBRRACE-UK, the collaboration responsible for the UK Confidential Enquiries into Maternal Death. Where a case

was identified, the UKOSS clinician was contacted and asked to complete a data collection form if appropriate.

It was not practicable to obtain consent for data collection from individual women with diagnosed PE. Names, addresses, postcodes, dates of birth and hospital numbers were therefore not collected in the UKOSS research platform, in accordance with guidance from the relevant regulatory bodies that organisations seeking to use information for research purposes without consent should not use any personally identifiable information.

Data collection

UKOSS clinicians and research nurses/midwives collected data from the hospitals records of the diagnosed and suspected PE groups respectively. We collected details of clinical features (including past medical history, previous pregnancies, current pregnancy, risk factors for VTE, presenting symptoms, clinical signs and physiological measures), D-dimer measurements (along with the laboratory reference standard), reports from diagnostic imaging, treatments for VTE, adverse events and any findings from surgery for PE or post-mortem.

The suspected PE group were also followed up at 30 days after recruitment by hospital record review and questionnaire survey to record any additional adverse events or health care. Where insufficient information was obtained to verify status at 30 days the woman's primary care physician was contacted and asked to provide details of additional investigations or events using primary care records.

Women recruited with suspected PE who were subsequently diagnosed with PE were cross-checked with the UKOSS cases to avoid duplication. In such cases data collected by the research nurses/midwives were used.

Index tests

Clinical features were classified *a priori* as present or absent, usually on the basis of the expected association between the feature and risk of having PE. For continuous variables we also identified a threshold to allow categorisation of the variable.

We tested three clinical decision rules that were developed through expert consensus in an earlier phase of the study.[11] These included a primary rule, in which the experts aimed for an optimal balance of sensitivity and specificity, along with sensitive and specific rules that optimised sensitivity and specificity respectively. Developing a clinical decision rule inevitably involves a trade-off between sensitivity (avoiding missing women with PE) and specificity (avoiding over-investigating women without PE). The three rules were developed to explore this trade-off with the primary rule intended to achieve high sensitivity without sacrificing specificity to the extent that nearly all women would be investigated. The expert derived decision rules are described in Appendix S1.

We took three existing clinical decision rules, the PERC rule,[6] the Well's PE criteria[7] and the simplified revised Geneva score,[8] and adapted them for a pregnant or postpartum population by using pregnancy-specific thresholds for age, oxygen saturation and heart rate, and removing exogenous oestrogen from the PERC rule. We also created two versions of the Well's criteria depending upon whether a strict or permissive interpretation was used for the criterion that an alternative diagnosis is less likely than PE.

D-dimer measurements were recorded for some women as part of routine care. Samples were analysed in different hospitals, using different assays with different diagnostic thresholds. Furthermore we expected specificity to decline with gestational age. We therefore planned to test a threshold for positivity for D-dimer using the hospital laboratory threshold during the first trimester, 1.5× the laboratory threshold for the second trimester and 2× the laboratory threshold for the 3rd trimester, based on data showing how D-dimer levels increase during pregnancy[12] and evidence that a higher threshold may improve specificity for diagnosing VTE in pregnancy without sacrificing sensitivity.[13]

Reference standard

Two independent assessors (SG,CNP), blind to clinical features and D-dimer measurements, used a structured process to classify diagnostic imaging results, adverse events and treatments, and thus classify all women as PE present or PE absent. This process was also used to determine whether they were included in the primary analysis (PE confirmed or ruled out by imaging, surgery or post-mortem) or secondary analysis (PE clinically diagnosed or ruled out). Details of the process are described in Appendix S2.

Sample size

The sample size was inevitably determined by the incidence of diagnosed and suspected PE during the data collection period. Based on a previous study[14] we anticipated that we would identify 150 cases with diagnosed PE over 18 months. We aimed to recruit 250 women with suspected PE over the same time period, resulting in about 155 cases with PE and 245 controls without, assuming prevalence of 2% in those with suspected PE. This would allow estimation of sensitivity or specificity of 90% with a standard error of about 2.5% and 2.0% respectively. Assuming that the ratio of cases to controls would be about 0.4, then this sample size would be sufficient to identify an odds ratio of a clinical predictor of about 2, with 90% power and 5% two sided significance.[15]

Analysis

Univariable logistic regression was used to determine the association between each clinical feature and the presence or absence of PE. Multivariate regression was performed adjusting for all other variables. Where the same variable was analysed in dichotomised and continuous form in the univariate analysis only the continuous variable was included in the multivariate analysis. Where "other" categories of previous medical problems and current pregnancy problems were classified as any other problem or VTE-related other problem in the univariate analysis only VTE-related categorisation was used in the multivariate analysis. We also tested the association between receipt of thromboprophylaxis and PE. Thromboprophylaxis is provided on the basis of VTE risk so it could be a marker for VTE risk, although it is intended to reduce VTE risk.

Diagnostic accuracy of each clinical decision rule was assessed by plotting a receiver-operator characteristic (ROC) curve and calculating the area under the curve (AUC). Sensitivity and specificity were calculated for each clinical decision rule using the recommended or standard threshold, and for D-dimer using the threshold outlined above. Univariable logistic regression and D-dimer analysis were limited to cases with complete data. For the clinical decision rule analysis missing variables in the rule were imputed as normal or negative, unless more than one of heart rate, respiratory rate and oxygen saturation were missing or more than half of the predictors relating to previous medical history or the current pregnancy were missing, in which circumstance the case was excluded.

Patient involvement

Patient representatives from Thrombosis UK and the Sheffield Emergency Care Forum advised on development of the protocol, reviewed all patient and public facing material and were members of the study steering committee.

Results

Between 1 March 2015 and 31 August 2016 we recruited 324 women with suspected PE across the prospectively recruiting sites. Screening identified an additional 35 women who were unable or unwilling to give consent and 95 who were eligible but not approached to participate. Over the same time period we identified 224 women with diagnosed PE through the UKOSS research platform. We excluded 21 who had or may have presented with life threatening features and five who were also identified through the suspected PE group, leaving 198 for analysis.

Figure S1 shows the flow of patients recruited and analysed in the study. And Table S1 shows the characteristics of the women with diagnosed PE, the recruited women with suspected PE and the women with suspected PE who were eligible but not asked to participate.

The 324 women with suspected PE consisted of 18 with PE confirmed by imaging, five with clinically diagnosed PE (three with equivocal imaging and two with no imaging; all treated), 259 with PE ruled out with imaging (254 with negative imaging and five untreated after equivocal imaging) and 42 with PE clinically ruled out without imaging (none treated). The 198 women with diagnosed PE consisted of 163 with PE confirmed by imaging or post-mortem (160 imaging, two post mortem and one both) and 35 with clinically diagnosed PE (29 with equivocal imaging and six with no imaging recorded; all treated). Thus the primary analysis population included 181 women with PE and 259 without PE.

Table 1 compares the characteristics between women with and without PE, and reports the univariate and multivariate odds ratio, 95% CI and *P*-value for each comparison. Table 2 reports the same analysis comparing presenting features, physiology, ECG and chest x-ray. There were few differences between the women with and without PE. The only features significantly associated with PE ($P < 0.05$) in univariate analysis were number of previous pregnancies beyond 24 weeks, surgery in the previous four weeks (including caesarean section), no history of varicose veins, no long haul travel during pregnancy, higher temperature, lower oxygen saturation and chest x-ray abnormality (both PE related and non PE related). In the multivariate analysis age (odds ratio 1.06; 95% confidence interval 1.01–1.11), previous thrombosis (3.07; 1.05–8.99), family history of thrombosis (0.35; 0.14–0.90), temperature (2.22; 1.26–3.91), systolic blood pressure (0.96; 0.93–0.99), oxygen saturation (0.87; 0.78–0.97) and PE-related chest x-ray abnormality (13.4; 1.39–130.2) were associated with PE. A higher proportion of women with PE had received thromboprophylaxis (88/181 (48.62%) versus 70/259 (27.03%) and receipt of thromboprophylaxis was associated with PE (odds ratio 2.56; 95% CI 1.72–3.82; $P < 0.001$). Table 3 compares the summary measures of each continuous clinical variable. There was little difference between women with and without PE.

Table 4 reports the diagnostic accuracy of each clinical decision rule and Figure S2 shows the ROC curve. Full results for each score are shown in Appendix S3. Diagnostic accuracy was generally poor. The sensitive expert consensus rule had good sensitivity (95%) but very poor specificity (4%), showing that sensitivity was only achieved by setting a very low threshold for positivity. The Well's PE criteria may have some modest diagnostic value if the criterion that an alternative diagnosis is less likely than PE is applied in a strict way, i.e. it is only positive if PE is clearly considered the most likely or equal most likely diagnosis. Figure S2 and Appendix S3

Table 1. Comparison of characteristics between women with and without PE

Basic demographics	Women with PE	Women without PE	Univariate odds ratio (95% CI)	Univariate *P*-Value	Multivariate odds ratio (95% CI)	Multivariate *P*-value
Age over 35 years	37 (20.44%)	40 (15.44%)	1.41 (0.86–2.31)	0.176	–	–
Age (continuous)	–	–	1.02 (0.99–1.05)	0.179	1.06 (1.01–1.11)	0.026
BMI 30 or more	60 (33.15%)	85 (32.82%)	1.01 (0.68–1.52)	0.942	–	–
BMI (Continuous)	–	–	1.01 (0.99–1.04)	0.372	1.03 (0.99–1.07)	0.153
Smoking Status						
Never	116 (64.09%)	171 (66.02%)	Reference	–	–	
Gave up before	28 (15.47%)	39 (15.06%)	1.06 (0.61–1.81)	0.837	1.09 (0.49–2.41)	0.828
Gave up during	23 (12.71%)	19 (7.34%)	1.78 (0.93–3.46)	0.082	2.35 (0.93–5.92)	0.070
Current	14 (7.73%)	30 (11.58%)	0.69 (0.34–1.33)	0.279	1.17 (0.44–3.10)	0.755
Previous pregnancies						
≥1 previous pregnancy <24 weeks	68 (37.57%)	97 (37.45%)	1.00 (0.68–1.49)	0.98	–	–
N of previous pregnancies <24 weeks (Continuous)	–	–	1.05 (0.91–1.23)	0.509	0.96 (0.79–1.18)	0.713
≥1 previous pregnancy >24 weeks	126 (69.61%)	165 (63.71%)	1.30 (0.87–1.97)	0.198	–	–
N of previous pregnancies >24 weeks (Continuous)	–	–	1.20 (1.04–1.30)	0.017	0.94 (0.72–1.22)	0.636
Previous Pregnancy Problems	55 (30.39%)	70 (27.03%)	1.18 (0.77–1.79)	0.442	1.17 (0.60–2.26)	0.646
Previous medical problems						
Family history of thrombosis	24 (13.26%)	46 (17.76%)	0.71 (0.41–1.20)	0.205	0.35 (0.14–0.90)	0.029
History of varicose veins	5 (2.76%)	19 (7.34%)	0.36 (0.12–0.91)	0.045	0.42 (0.09–1.86)	0.251
History of IV drug use	1 (0.55%)	1 (0.39%)	1.43 (0.06–36.4)	0.8	0	1.0
Known thrombophilia	4 (2.21%)	7 (2.70%)	0.81 (0.21–2.74)	0.745	0.12 (0.01–1.26)	0.077
Surgery in previous 4 weeks	35 (19.34%)	21 (8.11%)	2.72 (1.53–4.92)	0.001	0.85 (0.30–2.40)	0.753
Significant injury in the previous 4 weeks	2 (1.10%)	3 (1.16%)	0.95 (0.12–5.81)	0.959	0.42 (0.03–5.45)	0.505
History of thrombosis	19 (10.50%)	15 (5.79%)	1.91 (0.95–3.92)	0.073	3.07 (1.05–8.99)	0.041
Other previous medical problem	75 (41.44%)	110 (42.47%)	0.96 (0.65–1.41)	0.829	–	–
Other previous medical problem (VTE-related)	4 (2.21%)	6 (2.32%)	1.02 (0.26–3.62)	0.978	0.94 (0.16–5.61)	0.946
Current pregnancy						
1st Trimester	15 (8.29%)	20 (7.72%)	Reference	–	–	–
2nd Trimester	37 (20.44%)	79 (30.50%)	0.62 (0.29–1.37)	0.234	0.81 (0.28–2.30)	0.693
3rd Trimester	60 (33.15%)	116 (44.79%)	0.69 (0.33–1.46)	0.324	0.59 (0.21–1.64)	0.310
Post-Partum	63 (34.81%)	44 (16.99%)	1.91 (0.89–4.19)	0.101	1.63 (0.51–5.23)	0.407
Multiple pregnancy	4 (2.21%)	12 (4.63%)	0.47 (0.13–1.36)	0.191	0.13 (0.01–1.22)	0.074
Long-haul travel during pregnancy	2 (1.10%)	21 (8.11%)	0.13 (0.02–0.44)	0.006	0	1.0
3 or more days of immobility/bed rest	14 (7.73%)	21 (8.11%)	0.95 (0.46–1.91)	0.887	0.85 (0.29–2.54)	0.774
Previous thrombotic event this pregnancy	5 (2.76%)	3 (1.16%)	2.44 (0.59–1.20)	0.226	4.22 (0.49–36.1)	0.189
Other problems with this pregnancy	74 (40.88%)	73 (28.19%)	1.46 (0.97–2.20)	0.067	–	-
Other problems with this pregnancy (VTE-related)	15 (8.29%)	19 (7.34%)	1.14 (0.56–2.31)	0.713	1.05 (0.34–3.17)	0.938

show that there is no threshold for decision making that achieves high sensitivity without sacrificing specificity to an unacceptable degree.

D-dimer measurements were recorded as part of routine care for 44/198 (22%) women with diagnosed PE and 156/324 (48%) women with suspected PE. After exclusion of 22

Table 2. Comparison of presenting features, physiology, ECG and chest x-ray between women with and without PE

Presenting feature	Women with PE	Women without PE	Univariate odds ratio (95% CI)	Univariate *P*-Value	Multivariate odds ratio (95%CI)	Multivariate *P*-value
Presenting feature: Pleuritic chest pain	94 (51.93%)	137 (52.90%)	0.96 (0.66–1.41)	0.842	1.30 (0.69–2.45)	0.418
Presenting feature: Non-pleuritic chest pain	38 (20.99%)	47 (18.15%)	1.20 (0.74–1.93)	0.457	1.23 (0.57–2.67)	0.596
Presenting feature: Shortness of breath at rest	97 (53.59%)	157 (60.62%)	0.75 (0.51–1.10)	0.142	0.70 (0.40–1.24)	0.223
Presenting feature: Shortness of breath on exertion	93 (51.38%)	125 (48.26%)	1.13 (0.77–1.66)	0.52	1.60 (0.91–2.81)	0.104
Presenting feature: Haemoptysis	13 (7.18%)	10 (3.86%)	1.93 (0.83–4.61)	0.129	2.90 (0.84–10.1)	0.093
Presenting feature: Cough	16 (8.84%)	23 (8.88%)	1.00 (0.50–1.93)	0.988	0.38 (0.12–1.21)	0.102
Presenting feature: Syncope	9 (4.97%)	7 (2.70%)	1.88 (0.69–5.36)	0.218	2.79 (0.57–13.5)	0.203
Presenting feature: Palpitations	24 (13.26%)	30 (11.58%)	1.17 (0.65–2.07)	0.598	1.44 (0.53–3.87)	0.472
Presenting feature: Other	62 (34.25%)	90 (34.75%)	0.98 (0.65–1.46)	0.914	0.61 (0.32–1.17)	0.140
Temperature >37.5	14 (7.73%)	7 (2.70%)	3.02 (1.23–8.11)	0.02	-	-
Temperature (Continuous)			1.75 (1.22–2.57)	0.003	2.22 (1.26–3.91)	0.006
Diastolic <50 mmHg	4 (2.21%)	2 (0.77%)	2.90 (0.56–21.1)	0.221	-	-
Diastolic (Continuous)			1.01 (0.99–1.03)	0.256	1.03 (0.99–1.06)	0.122
Systolic <90 mmHg	3 (1.66%)	1 (0.39%)	4.35 (0.55–88.3)	0.205	-	-
Systolic (Continuous)			0.99 (0.98–1.01)	0.322	0.96 (0.93–0.99)	0.004
O2 Saturation <94%	27 (14.92%)	10 (3.86%)	4.37 (2.12–9.71)	<0.001	-	-
O2 Saturation (Continuous)			0.85 (0.78–0.92)	<0.001	0.87 (0.78–0.97)	0.012
Respiratory Rate >24/min	18 (9.94%)	25 (9.65%)	1.03 (0.54–1.95)	0.919	-	-
Respiratory Rate (Continuous)			1.00 (0.96–1.04)	0.948	0.94 (0.88–1.02)	0.136
Heart rate >100/min (110/min 3rd trimester)	55 (30.39%)	72 (27.80%)	1.13 (0.75–1.72)	0.556	-	-
Heart Rate (Continuous)			1.01 (0.99–1.02)	0.126	1.01 (0.99–1.03)	0.153
Clinical signs of DVT	23 (12.71%)	23 (8.88%)	1.49 (0.81–2.77)	0.199	1.63 (0.61–4.35)	0.325
PE related ECG abnormality	4 (2.21%)	8 (3.09%)	0.71 (0.19–2.29)	0.579	0.823 (0.40–1.69)	0.596
PE related chest x-ray abnormality	30 (16.57%)	18 (6.95%)	15.20 (2.82–282.0)	0.01	13.4 (1.39–130.2)	0.025
Other chest x-ray abnormality	9 (4.97%)	1 (0.39%)	2.82 (1.53–5.33)	0.001	2.49 (0.93–6.69)	0.069

Table 3. Comparison of continuous clinical variables between women with and without PE

Mean (SD)	Women with PE	Women without PE
Age (years)	30.2 (6.20)	29.4 (5.94)
BMI (kg/m^2)	28.7 (7.56)	28 (6.54)
Heart rate (/min)	98.3 (19.7)	95.5 (17.7)
Respiratory rate (/min)	19.0 (5.04)	19.0 (4.42)
Oxygen saturation (%)	96.5 (4.36)	97.8 (1.82)
Systolic BP (mmHg)	121 (17.0)	123 (15.7)
Diastolic BP (mmHg)	74.2 (12.3)	72.9 (11.7)
Temperature (degrees C)	36.8 (0.60)	36.6 (0.83)

women with clinically diagnosed or ruled out PE and 10 women with no D-dimer threshold recorded the primary analysis data set for those with routine care D-dimer measurements consisted of 43 women with PE and 125 without. The sensitivity and specificity (n/N, 95% CI) using the hospital laboratory threshold was 88.4% (38/43, 74.1–95.6) and 8.8% (11/125, 4.7–15.6) respectively. The sensitivity and specificity (95% CI) using the pregnancy specific threshold was 69.8% (30/43, 53.7–82.3) and 32.8% (41/125, 24.8–41.9) respectively.

The results of the secondary analyses are reported in Appendix S4. They showed no meaningful differences to the primary analysis.

Discussion

Main findings

We found that a number of risk factors for VTE have little diagnostic value and some may even be misleading when used in the diagnostic assessment of pregnant and postpartum women referred to hospital for suspected PE. History

Table 4. Diagnostic accuracy of the clinical decision rules

Decision rule	AUROC using full range of score values 95% CI	Sensitivity at usual or recommended threshold 95% CI n/N	Specificity at usual or recommended threshold 95% CI n/N
Primary consensus	0.626 0.572–0.681	0.609 0.532–0.683 103/169	0.585 0.523–0.646 151/258
Sensitive consensus	0.620 0.566–0.675	0.959 0.917–0.983 162/169	0.035 0.016–0.065 9/258
Specific consensus	0.589 0.537–0.642	0.361 0.289–0.438 61/169	0.783 0.728–0.832 202/258
PERC	0.621 0.570–0.672	0.675 0.598–0.745 114/169	0.519 0.457–0.582 134/258
Simplified Revised Geneva	0.579 0.526–0.632	0.444 0.368–0.522 75/169	0.636 0.574–0.694 164/258
Well's (permissive)*	0.577 0.522–0.632	0.490 0.410–0.571 77/157	0.617 0.553–0.678 153/248
Well's (strict)*	0.732 0.682–0.782	0.376 0.300–0.457 59/157	0.895 0.850–0.930 222/248

*Well's criteria were tested using a liberal (permissive) interpretation of clinical diagnosis text to determine whether PE was the most likely or equal most likely diagnosis and a more strict interpretation.

of varicose veins, family history of VTE and recent long haul travel are known risk factors for VTE but were more common in women with suspected PE who had PE ruled out than those with diagnosed PE, although only family history of VTE was associated with absence of PE on multivariate analysis. It is possible that the presence of risk factors led to an increased likelihood of presentation to or referral to secondary care. Presenting clinical features were unhelpful in diagnosing PE, while oxygen saturation, systolic blood pressure and temperature were the only physiological measures associated with PE. Chest x-ray abnormalities that were not considered to be PE-related were more frequent in women with PE, although only PE-related abnormalities were associated with PE on multivariate analysis. These findings suggest that we need to reconsider the way we interpret the clinical assessment of pregnant or postpartum women attending hospital with suspected PE.

We also found that existing clinical decision rules have little discriminant value in the assessment of suspected PE in pregnancy and postpartum. The AUCs for all but one of the rules were close to 0.5 indicating discriminant value little better than chance. Only the Well's PE criteria with a strict interpretation of whether PE was the most likely or equal most likely diagnosis showed meaningful discriminant value. Previous studies[16,17] suggested that the Well's PE criteria could be used to rule out PE in pregnancy, albeit based on small numbers with PE and imprecise estimates of sensitivity. Our study included many more cases with PE and showed that sensitivity was inadequate to rule out PE. The rules had sensitivities between 0.361 and 0.675 (apart from the sensitive rule) indicating that they would miss between one and two thirds of cases of PE. The sensitive rule had acceptable sensitivity to rule out PE but with specificity of 0.035 would not allow a rule-out for a meaningful proportion without PE.

Finally we have shown that D-dimer is unable to discriminate between pregnant and postpartum women who have PE and those who do not. At both thresholds for positivity tested the sensitivity was similar to one minus the specificity. This indicates that the proportion with a positive D-dimer is similar in those with and without PE. Previous studies of D-dimer in pregnant women with suspected PE produced mixed results and imprecise

Table 5. Implementation of the clinical decision rules and D-dimer

Assessment	PE correctly identified (true positive)	PE missed (false negative)	PE correctly ruled out (true negative)	PE incorrectly diagnosed (false positive)
Primary consensus rule	40	25	547	388
Sensitive consensus rule	62	3	33	902
Specific consensus rule	23	42	732	203
PERC rule	44	21	485	450
Simplified Revised Geneva score	29	36	595	340
Well's score (permissive)	32	33	577	358
Well's score (strict)	24	41	837	98
D-dimer (conventional threshold)	57	8	82	853
D-dimer (pregnancy-specific threshold)	45	20	307	628

The table shows how a population of 1000 women, of whom 65 had PE, would be classified by the clinical decision rules and D-dimer.

estimates of accuracy,[16–19] but studies of suspected DVT in pregnancy suggested high sensitivity[20] and acceptable specificity if a higher threshold for positivity was used.[13] Our study provides more precise estimates of accuracy for PE in pregnancy and suggests that D-dimer has no useful role in diagnosis.

Table 5 shows how the clinical decision rules and D-dimer would classify a population of 1000 women with suspected PE, of whom 65 had PE (based on the prevalence in the primary analysis population with suspected PE). All except the sensitive consensus rule and D-dimer would miss a substantial proportion of cases with PE, and both of these would be positive in a greater proportion of those without PE than those with PE.

It is important to recognise that our findings apply to the diagnostic assessment of suspected PE in pregnant and postpartum women referred for hospital investigation. They may reflect the processes used to select women for hospital investigation. For example, if women with minor symptoms and a recent history of long haul travel decide to attend or are advised to attend hospital while those with similar symptoms but no such history self-manage or seek care elsewhere, then this may explain why recent long haul travel appears to predict absence of PE in secondary care. Our study was not intended to identify risk factors for VTE in pregnancy and postpartum, so our findings should not be interpreted as challenging current knowledge about risk factors in pregnancy and postpartum, only their use as diagnostic markers in those receiving hospital investigation of suspected PE.

Strengths and limitations

The key strength and rationale for the study design was the large number of women with PE. We were able to estimate associations and diagnostic parameters with much greater precision than previous studies. We identified women with diagnosed PE from all UK hospitals with consultant-led maternity units and recruited women with suspected PE from a range of different settings, thus ensuring the generalisability of our findings.

The increased power for measuring sensitivity came with an increased risk of bias, as seen in case-control studies.[10] We attempted to minimise this by ensuring that the additional cases were representative of all diagnosed PE, not just the most severe cases, and that women without PE were representative of women presenting with suspected PE in whom the diagnosis is subsequently ruled out. The design related bias associated with case-control studies tends to inflate estimates of diagnostic accuracy, so would not undermine our conclusions that clinical features, decision rules and D-dimer have little diagnostic value. However, in our study design related bias may have had the opposite effect. Although we asked research nurses to collect data from hospital records rather than the patient it is possible that they were able to use prospective data to more accurately identify clinical features (such as long haul travel and varicose veins) than the UKOSS clinicians who were entirely reliant upon hospital records.

Our evaluation of clinical decision rules was limited by the need to adapt existing rules to the pregnant and postpartum population and apply the rules retrospectively to the study data. This led to a number of assumptions and interpretations, most notably in the application of the Well's criterion "Is PE the most likely or equally most likely diagnosis?" This was determined by interpreting the text of the clinical diagnostic impression. Although we attempted to ensure that this was the diagnostic impression recorded before imaging it is possible than in some cases of diagnosed PE this was recorded after imaging. The apparent diagnostic superiority of Well's PE criteria over other

clinical decision rules is highly dependent on this criterion so conclusions regarding the relative performance of the Well's PE criteria should be made with caution. Conversely, all of the rules may perform better if used prospectively rather than being retrospectively applied to collected data.

Interpretation

The practical implication of this study is that women presenting to secondary care with PE in pregnancy or postpartum suspected by their treating clinician should all receive imaging for PE. Although 42/324 (13%) of the women with suspected PE did not receive imaging the lack of adverse outcome in this modest number of cases provides little reassurance that they were safely managed. In the absence of a structured and validated means of selecting women for imaging we would expect guidelines to recommend imaging for all.

Further research is required to estimate the risks and benefits of imaging for PE in the pregnant and postpartum population and develop ways for clinicians to present this information to women in a comprehensible manner. Biomarkers other than D-dimer may be of value and could be the subject of future study. However, further research into clinical decision rules and D-dimer are unlikely to be worthwhile. The limitations of our study design are unlikely to explain the negative findings, suggesting that the effort and expense required to deliver a prospective cohort study is unlikely to be justified.

Conclusion

Clinical features, existing clinical decision rules and D-dimer have little diagnostic value and should not be used to select pregnant or postpartum women with suspected PE for diagnostic imaging. Chest x-ray abnormality, even if not considered to be PE-related, increases the likelihood of PE diagnosis.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

SG was the Chief Investigator for the DiPEP study and KH the Project Manager. The study was designed by SG, CNP, BJH, MK, ST and FL. KH was responsible for recruitment and data collection from women with suspected PE. MK was responsible for data collection from women with diagnosed PE identified through UKOSS. NS undertook the statistical analysis. SG, KH, CNP, MK, NS, FL, ST, BJH and GF contributed to management of the project and interpretation of the data. SG wrote the initial draft of the paper. SG, KH, CNP, MK, NS, FL, ST, BJH and GF contributed to redrafting and approved the final draft of the paper. SG is guarantor for the paper.

Details of ethics approval

The study was approved by the London Brent Research Ethics Committee (reference 14/LO/1695) on 10 October 2014. Written consent was obtained from women with suspected PE. Only anonymised data were collected from women with diagnosed PE so consent was not sought.

Funding

The DiPEP study was funded by the United Kingdom National Institute for Health Research Health Technology Assessment (HTA) programme (project reference 13/21/01). The research question was prioritised by the HTA programme commissioning process with patient and public involvement. Funding was granted following a competitive commissioning process that included external peer review for scientific quality. The funder played no subsequent role in conducting the research or writing the paper.

Acknowledgements

We thank all members of the DiPEP research group for their invaluable assistance in delivering this project and who are detailed in Appendix S5.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Recruitment flow and analysis populations.

Figure S2. ROC curves for clinical decision rules.

Table S1. Characteristics of the study groups.

Appendix S1. Expert consensus derived clinical decisions rules for pregnant and postpartum women with suspected PE.

Appendix S2. Reference standard classification.

Appendix S3. Diagnostic performance of the clinical decision rules.

Appendix S4. Results of secondary analyses.

Appendix S5. The DiPEP Research Group. ■

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