

BET 2: CURRENT EVIDENCE DOES SUPPORT THE USE OF A NEGATIVE D-DIMER TO RULE OUT SUSPECTED PULMONARY EMBOLISM IN PREGNANCY

Report by: Sally Rhead, *Medical Student*

Checked by: Craig Ferguson, *Consultant*

Institution: Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK

ABSTRACT

A short cut review was carried out to establish whether a negative D-dimer could be used to rule out pulmonary embolism in the presence of clinical suspicion in a pregnant patient. Five studies were considered directly relevant to the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes and study weaknesses were tabulated. The clinical bottom line was that a negative D-dimer result was considered sensitive enough to rule out pulmonary embolism in patients who were in the first two trimesters of pregnancy but that the false positive rate was so high as to render the test useless in patients in the third trimester if standard cut-off values were used.

THREE PART QUESTION

In (a clinically well pregnant patient with a suspected pulmonary embolism) is (a negative D-dimer sensitive enough) to (exclude pulmonary embolism).

CLINICAL SCENARIO

A 24-year-old woman who was 20 weeks pregnant presented to the Emergency Department with shortness of breath and pleuritic chest pain. Her Well's score is calculated at moderate. You wonder if a negative D-dimer result would be sensitive enough to rule out pulmonary embolism (PE).

SEARCH STRATEGY

Database: Evidence Based Medicine (EBM) Reviews—Cochrane Database of Systematic Reviews <2005 to May 2014>, Embase <1980 to 2014 Week 27>, Ovid MEDLINE (R) <1946 to July Week 1 2014>

SEARCH STRATEGY

[pulmonary embolism.mp. OR exp Pulmonary Embolism OR venous

thromboembolism.mp. OR exp Venous Thromboembolism OR pe.af OR vte.af OR pulmonary embolism.af. OR venous thromboembolism.af.] AND [pregnant women.mp. OR exp Pregnant Women OR exp Pregnancy/OR pregnan\$.af OR exp Pregnancy Complications] AND [fibrin fibrinogen degradation products.mp. OR exp Fibrin Fibrinogen Degradation Products OR cross-linking reagents.mp. OR exp Cross-Linking Reagents OR D-dimer.mp. OR FDP.mp. OR fibrin fibrinogen degradation products.af. OR cross-linking reagents.af. OR D-dimer.af. OR FDP.af.] LIMIT to English language and female and humans.

SEARCH OUTCOME

Four hundred and ninety-five papers were found of which a total of 5 papers were considered relevant to the three-part question (see [table 2](#)).

COMMENT(S)

D-dimer values are successfully used to rule out venous thromboembolism (VTE) in non-pregnant patients due to their high sensitivity. There are now several studies demonstrating that D-dimer levels increase throughout pregnancy even in women with no signs or symptoms suggestive of thromboembolic disease. In theory this should mean that pregnant women with D-dimer levels below the standard cut-off values have even less chance of having a VTE than the general population.

Damodaram *et al* (2009) concluded that D-dimers were not useful in ruling out PE in pregnancy. This study used a small sample size and used VQ scans as the reference standard, with moderate probability scans considered positive. The other studies showed high sensitivity for D-dimers but suggested pregnancy-specific cut-off values to improve the specificity of the test. No studies were found that validated novel cut-off values for use in pregnant patients.

There is a consistent finding in all of the studies that D-dimer values are raised in pregnancy. It could therefore be extrapolated that current D-dimer levels would be more sensitive in pregnant women than in non-pregnant women as they are more likely to already have higher D-dimers. A negative D-dimer in this group would be highly suggestive that the patient does not have a PE unless there is strong clinical suspicion. It is important to use clinical judgement also as there has been a case report (To, 2008) of a pregnant patient with recurrent PE and normal D-dimer results although this patient had already been commenced on long-term heparin at this time due to

clinical suspicion of VTE and a positive D-dimer test earlier in her pregnancy.

The included studies also found that applying current diagnostic thresholds for D-dimers in patients in the third trimester were of no value as only 0–1% of these patients had a normal D-dimer level at this stage regardless of whether they have a PE or not.

D-dimer levels are usually only used in conjunction with a clinical predictive assessment which in the case of VTE in non-pregnant patients is the Well's score. D-dimer testing is used in patients with a moderate pretest probability to decide if further testing is needed. Although the Wells' score has not been validated in pregnant women it does appear to be a useful tool in calculating pretest probability, as its categories remain relevant. The evidence above indicates that D-dimer values can be used in combination with this scoring system during first and second trimesters to either rule out PE or indicate the need for further diagnostic investigations.

Clinical bottom line

Current evidence supports the use of a D-dimer testing to rule out pulmonary embolism in pregnant patients in their first or second trimester.

- ▶ Kline J, Williams G, Hernandez-Nino J. D-dimer concentrations in normal pregnancy@ new diagnostic thresholds are needed. *Clin Chem* 2005;51:825–9.
- ▶ To M, Hunt B, Nelson-Piercy. A negative D-dimer does not exclude venous thromboembolism (VTE) in pregnancy. *J Obstet Gynaecol* 2008;28:222–40.
- ▶ Damodaram M, Kaladindi M, Luckit J, *et al*. D-dimers as a screening test for venous thromboembolism in pregnancy: Is it of any use? *J Obstet Gynaecol* 2009;29: 101–3.
- ▶ Nishii A, Noda Y, Nemoto R. Evaluation of D-dimer during pregnancy. *J Obstet Gynaecol* 2009;32:689–93.
- ▶ Chan W, Lee A, Spencer F. D-dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis. *J Thromb Haemost* 2010;8: 1004–11.
- ▶ Kovac M, Mikovic Z, Rakicevic L, *et al*. The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. *Eur J Obstet Gynaecol Reprod Biol* 2010;148:27–30.

Provenance and peer review Commissioned; internally peer reviewed.

Emerg Med J 2014;31:946–947.
doi:10.1136/emered-2014-204290.2

Table 2 Relevant papers

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Weaknesses
Kline <i>et al</i> , 2005, USA	50 healthy women who indicated desire to become pregnant	Prospective observational cohort study	Percentage of women below the D-dimer reference range 0.50 mg/L	Preconception 79% 1st trimester: 50% 2nd trimester: 22% 3rd trimester: 0%	High number lost in follow-up, only 23 completed all 4 blood tests Patients recruited at a preconception obstetric appointment and so may already be high risk
Damodaram <i>et al</i> , 2009, UK	37 pregnant patients suspected of VT who underwent a V/Q scan and D-dimer test	Retrospective cohort study	Sensitivity of D-dimer test Specificity of D-dimer test	0.73 0.15	Small, retrospective study. Reference standard was a V/Q scan, moderate or high probability was considered positive. Slight discrepancy in result totals.
Nishii <i>et al</i> , 2009, Japan	1131 pregnant women	Prospective observational cohort study	Mean and SE of D-dimer D-dimer difference between singleton and twin pregnancies Mean D-dimer related to ultrasound in 3rd trimester (n=1078) Predictive values when D-dimer reference 3.2 µg/mL	1st trimester: 1.1±1.0 µg/mL 3rd trimester: 2.2±1.1 µg/mL 1st trimester: not significant 3rd trimester: Singleton—2.2±1.6 µg/mL Twin—3.7±2.5 µg/mL Positive ultrasound D-dimer: 2.6±2.0 µg/mL Negative ultrasound D-dimer: 2.2±1.6 µg/mL (statistically significant) Positive: 7.4% Negative: 95.5%	Limited data provided so unable to calculate sensitivity and specificity of standard or proposed reference ranges.
Chan <i>et al</i> , 2010, Canada	228 pregnant women with suspected DVT	Prospective observational cohort study	Standard and suggested cut-off values in pregnancy against ultrasound for DVT.	Vidas, Asserachrome, IL Test, STA-Lisa and Innovance assays all had 100% sensitivity with standard cut-off values and variable, but poor levels of specificity (6–23%).	Patients with signs of PE were excluded
Kovac <i>et al</i> , 2010, Serbia	89 healthy pregnant women and 12 pregnant women with clinical suspicion of VTE	Prospective observational cohort study	Percentage of women below the D-dimer normal reference range 230 ng/mL Suggested D-dimer cut-off ranges (mean value plus one SD) Sensitivity of new cut-off ranges in 12 women suspected of VTE	1st trimester: 84% 2nd trimester: 33% 3rd trimester: 1% 1st trimester: 286 ng/mL 2nd trimester: 457 ng/mL 3rd trimester: 644 ng/mL 100% (0 women had VTE with D-dimer <230 ng/mL)	Numerous exclusion criteria. Small study. 10 of the 12 patients had a DVT, none had a PE.

DVT, deep vein thrombosis; PE, pulmonary embolism; VQ, A ventilation/perfusion lung scan; VTE, venous thromboembolism.



BET 2: Current evidence does support the use of a negative D-dimer to rule out suspected pulmonary embolism in pregnancy

Emerg Med J 2014 31: 946-947
doi: 10.1136/emered-2014-204290.2

Updated information and services can be found at:
<http://emj.bmj.com/content/31/11/946>

Email alerting service *These include:*
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections Articles on similar topics can be found in the following collections
[Pulmonary embolism](#) (101)
[Venous thromboembolism](#) (151)

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>