

Rural Healthcare *Quality* Network
Hospital Peer Review

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Hospital Peer Review is a monthly newsletter sponsored by the Rural Healthcare Quality Network to alert Critical Access Hospitals regarding findings from the Peer Review Program. Summarized are a few of the key findings and best practices that would be helpful for other critical access hospitals to be knowledgeable about. This newsletter is edited by Myron Bloom, Medical Director and he can be reached at drmbloom@msn.com.

D-dimer to rule out VTE in Pregnancy

During Pregnancy the haemostatic balance is changed in the direction of hypercoagulability, resulting in a 5- to 10- fold higher risk of venous thromboembolism (VTE) with an overall incidence of 1 per 1000 pregnancies.

The risk of VTE is increased throughout pregnancy and is particularly high following the delivery. Unfortunately the clinical diagnosis of VTE in pregnancy is unreliable, because symptoms like dyspnea and leg swelling are common features of an otherwise normal pregnancy. Furthermore, compression ultrasonography, the primary diagnostic tool for DVT does not reliably detect isolated iliac vein or calf vein thrombosis. Therefore, an objective, quick, and non-invasive test like D-dimer is useful to determine if a pregnant woman is at increased risk of VTE.

Normal pregnancy causes the maternal plasma D-dimer concentration to increase progressively from conception through delivery confounding the use of non-pregnant normal D-dimer values to rule out suspected venous thromboembolism in symptomatic pregnant patients. By the beginning of the second trimester, more than half of pregnant women will have a D-dimer concentration that exceeds 0.50 mg/L and by the third trimester more than 90% of women will have a D-dimer concentration .0.50 mg/L or more.

In a multicenter database of 4653 emergency department patients tested for a possible pulmonary embolism, 154 patients were pregnant (3.3%), and only 6 of the 154 (3.8%) were actually diagnosed with pulmonary embolism. Studying 50 pregnant women (of whom blood samples were obtained at preconception and all trimesters from 23), Hernandez & Kline found that pregnancy increased the D-dimer concentration in a stepwise fashion from preconception to the third

trimester with a 39% relative increase in D-dimer concentration for each trimester compared with the previous measurement (0.43 mg/L at preconception and 0.58, 0.83, and 1.16 mg/L in the first, second, and third trimesters, respectively). Only 22% of women in the second trimester and none (of the 23) in the third trimester had a D-dimer concentration <0.50 mg/L. [D-Dimer Concentrations in Normal Pregnancy: New Diagnostic Thresholds Are Needed, *Clinical Chemistry* 51:5 825–829 (2005)]

1131 pregnant women were enrolled in a study from April 2006 to March 2007, utilizing a latex immunoassay at 6 to 14 and 30 to 36 weeks of gestation as well as lower extremity ultrasound at 30 to 36 weeks of gestation. D-dimer significantly increased during pregnancy with mean and standard error of D-dimer of 1.1 +/- 1.0 microg/mL in the first trimester and 2.2 +/- 1.1 microg/mL in the third trimester. D-dimer was not significantly different between singleton and twin pregnancies in the first trimester, but in the third trimester, the values of twin pregnancies were higher than singleton pregnancies (2.2 +/- 1.6 vs. 3.7 +/- 2.5 microg/mL). The mean value of D-dimer of ultrasonographically positive women was 2.6 +/- 2.0 microg/mL, which was significantly higher than the value for an US negative woman during the third trimester (2.2 +/- 1.6 microg/mL). The positive predictive value was calculated to be 7.4% and negative predictive value was 95.5% for ultrasonographically positive women when D-dimer was set at 3.2 microg/mL. They proposed that women with D-dimer higher than 3.2 microg/mL should be closely monitored for prevention of pulmonary thromboembolism. [Nishii A, et al, Evaluation of D-dimer during pregnancy. *J Obstet Gynaecol Res.* 2009 Aug; 35(4):689-93.]

In a study by Morse, 48 pregnant healthy women (aged 17–36 years, 21 nulliparous, 20 primiparous and seven multiparous, and 34 women non-pregnant as a control group) were studied (IL D-dimer; Instrumentation Laboratory, Milan, Italy), sequentially during their pregnancy to identify the normal D-dimer levels in pregnancy. Significant differences were not found between the control group compared to pregnant women prior to 16 weeks, so it was felt that their usual reference range of <280 ng mL could still be for used up to 16 weeks gestation. Significantly elevated results were noted after 16 weeks, so using statistical methods, then they defined two further ranges for 16–26 weeks (< 465 ng mL) and 27–34 weeks (< 640 ng mL) gestation. [Morse M. Establishing a normal range for D-dimer levels through pregnancy to aid in the diagnosis of pulmonary embolism and deep vein thrombosis. *J Thromb Haemost* 2004; 2: 1202–4.]

Another prospective study found very similar results by following 101 pregnant women (89 healthy and 12 with clinical suspicion of VTE) using a quantitative latex immunoagglutination D-dimer assay with reference value of 230 ng/mL. They found that in the first trimester 84% had a “normal” D-dimer, in the second 33%, and by the third trimester only 1% had “normal” D-dimer using their usual laboratory reference “normal” value. The mean D-dimer concentration in the first trimester was 222 ng/mL, in the second of 326 and in the third of 475 ng/mL,

indicating a 46% increase of D-dimer concentration, from 12 to 24, and again from 24 to 34 weeks of gestation. They found all pregnant women with thrombosis diagnosed by positive ultrasound findings also had statistically significant elevation of the D-dimer level compared to values they adjusted for pregnancy term resulting in a 100% sensitivity of the D-dimer. They found that a women who developed thrombosis in the first trimester had 6.7–7.6 time higher level of D-dimer, and in the third trimester thrombotic women had 2.0– 3.8 time higher level of D-dimer, $p < 0.0001$. Using that D-dimer assay they proposed new thresholds of 286 for the first, 457 for the second of and 644 ng/mL for the third trimester in a workup of pregnancy related VTE. [Mirjana Kovac et al; The use of D-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy, *European Journal of Obstetrics & Gynecology and Reproductive Biology* 148 (2010) 27–30]

In an 8 year long study enrolling 249 pregnant women who presented with suspected DVT, 15 (6.6%) were diagnosed with DVT. Plasma was collected and available for 5 different assay testing in 228 of these patients (2 of the 21 patients who did not have D-dimer levels measured had DVT). The majority presented with suspected DVT in the second (36.4%) or third (59.6%) trimesters of pregnancy, with the distribution of DVT diagnosed being 26.6%, 26.7% and 46.7%, respectively, in the first, second and third trimesters of pregnancy. DVT was diagnosed on initial presentation in 80% (12/15) of patients; but of the remaining 3 patients, DVT was diagnosed on serial testing over 7 days. The first patient initially had a great saphenous vein thrombosis, which progressed into the femoral vein over 6 days, the second patient had two negative compression ultrasonography results, followed by a positive third compression ultrasonography result on day 7 that demonstrated extensive DVT involving the ileofemoropopliteal veins, and the third patient had a popliteal vein DVT diagnosed 4 days after the initial negative ultrasound result. However, no patients developed PE during follow-up. As expected, the D-dimer levels increased with each trimester of pregnancy among women who did not have acute thrombosis, but D-dimer values were also significantly higher in those women who were diagnosed with DVT than in those who were not in each of the five different assay tests. Besides identifying cases of DVT initially missed by ultrasound testing, they showed that even though D-dimer levels increased several-fold during pregnancy, using higher D-dimer cut-points could be used to exclude DVT. [Chani WS et al, D-dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis *Journal of Thrombosis and Haemostasis* Volume 8, Issue 5, pages 1004–1011, May 2010]

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D-Dimer levels are known to be elevated in pregnancy. But how high is too high and can this test be used in the workup of VTE in pregnant patients?

Recent literature indicates that D-dimer levels in each of the three trimesters are approximately 39% higher: 700, 1000, and 1400 ng/dL for each trimester (normal cutoff 500 ng/dL). So, figure out what trimester your patient is in and use the corresponding D-Dimer level for that trimester.

Hernandez J, Hambleton G, Kline JA. D-dimer concentrations in normal pregnancy. Acad Emerg Med 2004;11:526-527

And here is a similar adjustment for age

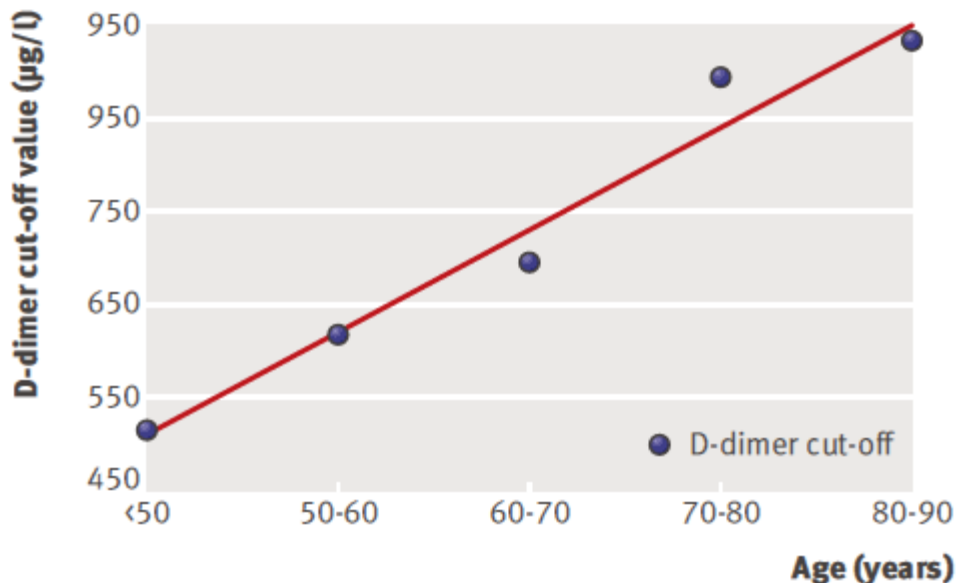


Fig 1 | Optimal cut-off values for D-dimer test for pulmonary embolism by age in patients with an unlikely clinical probability of pulmonary embolism (sensitivity set at 100%)

Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts BMJ 2010; 340:c1475