

A Red Blood Cell Agglutination D-Dimer Test to Exclude Deep Venous Thrombosis in Pregnancy

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Background: D-Dimer testing is often used with compression ultrasonography for the diagnosis of deep venous thrombosis (DVT) in nonpregnant patients. The D-dimer test is highly sensitive, and a negative result can obviate the need for further testing for DVT. This test has not been studied for DVT diagnosis in pregnancy because its specificity was deemed too poor.

Objective: To determine the sensitivity and specificity and assess the utility of the SimpliRED assay (Agen Biomedical, Brisbane, Australia) for the diagnosis of DVT in pregnant women.

Design: Prospective cohort study.

Setting: 5 tertiary university-affiliated Canadian hospitals providing care to obstetric patients.

Patients: 149 consecutive pregnant women with suspected DVT who presented to 1 of the participating centers over 5 years.

Intervention: Participating women were tested with compression leg ultrasonography (single or serially on days 0, 3, and 7) and received 3 months' clinical follow-up for the presence or absence of DVT. Whole blood was tested with the SimpliRED assay at initial presentation, and results were correlated with ultrasonography and clinical findings for the presence or absence of DVT.

Measurements: The sensitivity, specificity, and negative predictive value of the SimpliRED assay were calculated, along with the prevalence of false-positive SimpliRED assay results (with 95% CIs).

Results: The prevalence of DVT in the cohort was 8.7% (95% CI, 5.2% to 14.4%). The sensitivity of the SimpliRED assay was 100% (CI, 77% to 100% [13 of 13 patients]), the specificity was 60% (CI, 52% to 68% [81 of 135]), and the negative predictive value was 100% (CI, 95% to 100% [81 of 81]). The SimpliRED assay was positive in 0% (CI, 0% to 60%), 24% (CI, 14% to 37%), and 51% (CI, 40% to 61%) of women in the first, second, and third trimesters, respectively, among pregnant patients in whom DVT was not diagnosed.

Limitations: The prevalence of DVT in the cohort was low, resulting in wide CIs. The clinician's previous impression was used to determine pretest probability in the absence of a validated clinical prediction rule for pregnant women.

Conclusion: The SimpliRED assay may be useful in pregnancy because a normal result excludes DVT and occurs frequently enough to be clinically helpful.

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Venous thromboembolism (VTE) remains a major cause of maternal morbidity and mortality in developed countries (1–5), and deep venous thrombosis (DVT) is its most common manifestation. Although the overall incidence of VTE among pregnant women is low—fewer than 1 per 1000 pregnancies (5, 6)—this represents a 3- to 4-fold increased risk for VTE compared with age-matched nonpregnant women. As in nonpregnant women, clinical assessment alone is inaccurate for the diagnosis of DVT in symptomatic pregnant patients. The diagnosis of DVT in pregnant patients is further confounded by the frequent occurrence of nonthrombotic causes of leg swelling and pain and the lack of studies evaluating the accuracy of diagnostic testing for DVT.

The primary diagnostic tool for DVT is compression ultrasonography (7). This test has been validated as highly sensitive and specific for detecting clinically important DVT in nonpregnant persons. However, the test does not reliably detect isolated iliac vein thrombosis, which is thought to occur relatively frequently during pregnancy (8, 9), or calf vein thrombosis (7). In addition to compression ultrasonography, diagnostic algorithms involving the assessment of clinical pretest probability and D-dimer testing have been developed to guide clinicians in the management of nonpregnant patients suspected of having DVT (10–13). These algorithms call for D-dimer testing before the

use of compression ultrasonography to stratify patients into those who do and do not require further diagnostic testing. These studies have improved the clinician's ability to accurately diagnose DVT at presentation (10–13).

Unfortunately, none of the pivotal studies that provided the evidence to generate the algorithms included pregnant patients suspected of having DVT (10–13). Compression ultrasonography has been widely adopted as the diagnostic test of choice in pregnant women (14) because of its accuracy in the nonpregnant population and its relative safety with respect to the fetus. The use of D-dimer testing (with or without assessment of the clinician's earlier impression to determine pretest probability) has not been studied in pregnant women suspected of having DVT. In nonpregnant patients, a normal D-dimer test result excludes DVT when combined with either a low pretest probability (as assessed by using a structured clinical pre-

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Context

Because D-dimer levels increase with pregnancy, D-dimer testing is thought to be less accurate for excluding venous thromboembolism in pregnant women than in nonpregnant women.

Contribution

In this observational, cross-sectional study of 149 pregnant women with suspected deep venous thrombosis (DVT), 13 women (8.7%) had documented DVT. All 13 women with DVT had a positive result on the SimpliRED D-dimer assay (sensitivity, 100% [95% CI, 77% to 100%]).

Cautions

The lower bound of the 95% CI for the sensitivity of the SimpliRED assay was relatively low (77%). Caution is indicated when the assay is negative and clinical suspicion is relatively high.

Implications

The SimpliRED assay appears to be as useful for evaluating suspected DVT in pregnant women as in nonpregnant women. A normal result excludes the diagnosis.

—The Editors

diction rule) or a normal result on compression ultrasonography (10–13). D-Dimer levels increase as a normal pregnancy progresses and spike when such conditions as placental abruption or preeclampsia complicate a pregnancy (15, 16). Consequently, the D-dimer test is likely to have lower specificity during pregnancy and therefore produce more false-positive results.

Several studies (17–19), including one of our own (17), have investigated the performance in asymptomatic pregnant women of various D-dimer assays that were previously validated for VTE diagnosis in nonpregnant patients (20, 21). Both rapid enzyme-linked immunosorbent assay (ELISA) D-dimer tests and latex agglutination tests, at current cutoff values, demonstrated limited diagnostic usefulness in pregnant women suspected of having DVT. In the case of the rapid ELISA, most asymptomatic pregnant women had D-dimer levels that exceeded the reference limit (<280 ng/mL) after 16 weeks of gestation (18). In the case of 1 latex agglutination assay, only 22% of women in the second trimester and none in the third trimester had levels less than the reference limit of 0.5 mg/L (19). In contrast, results on the SimpliRED assay (Agen Biomedical, Brisbane, Australia) were negative in at least 75% of pregnant women without DVT in the first 2 trimesters of pregnancy and in half of the women by the third trimester.

In addition to having higher specificity in pregnancy, the SimpliRED assay is relatively easy to perform. Whole blood is mixed with a conjugate of monoclonal antibody to D-dimer linked to a monoclonal antibody, which binds to the erythrocyte surface. The conjugate will coat the eryth-

rocytes, causing agglutination if D-dimer levels are high (22). The presence or absence of agglutination can be interpreted by experienced personnel and the results made available in minutes.

Because the SimpliRED assay has a relatively high negative predictive value for DVT in nonpregnant patients (20), has a relatively low rate of false-positive results in asymptomatic pregnant patients (17), and is easy to use (there is no need for specialized equipment), we assessed the accuracy of this assay for excluding DVT and investigated its clinical utility in pregnant women suspected of having DVT.

METHODS**Study Sample**

Consecutive pregnant women presenting to 5 Canadian centers between March 2000 and November 2005 who were suspected of having DVT were potentially eligible for the study. The 5 centers were Women's College Hospital, Toronto (center 1); Hamilton Health Sciences, McMaster University Medical Center Site (center 2); Henderson Hospital Site (center 3); St. Joseph's Healthcare Centre, Hamilton (center 4); and Ottawa Hospital Civic and General Campuses, Ottawa (center 5). The Hamilton and Ottawa centers are tertiary referral sites for thrombosis; the Toronto site, McMaster, St Joseph's, and the Ottawa sites are tertiary referral centers for pregnant women.

Patients with 1 or more of the following were excluded: a history of VTE, treatment with "full-dose" anticoagulation for more than 24 hours, concomitant symptoms consistent with pulmonary embolism (PE), inability or unwillingness to return for follow-up, geographic inaccessibility, and failure of patient or attending physician to provide consent.

Study Flow

The protocol was reviewed and approved by the ethics research boards of all participating centers. Written informed consent was obtained from all study participants. All patients had compression ultrasonography of the symptomatic legs at presentation. Compression ultrasonography was performed with gentle compression of the deep veins of the legs, including the common femoral, the superficial femoral, the popliteal, and the calf trifurcation. If isolated iliac vein thrombosis was suspected, the iliac vein was visualized by direct imaging and Doppler flow. If the result of initial compression ultrasonography was negative, some patients had repeated compression ultrasonography on days 3 and 7, based on the clinician's standard of practice. Deep venous thrombosis was diagnosed on the basis of a noncompressible venous segment and, for the iliac veins, the absence of flow in the iliac vein or the presence of a visible thrombus by B-mode imaging. All patients with DVT were treated with unfractionated or low-molecular-weight heparin. Patients whose result on compression ultrasonography was normal had anticoagulant therapy with-

held and underwent clinical follow-up for at least 3 months to ensure the correctness of the initial exclusion of DVT. This approach has been used to categorize patients as DVT positive or DVT negative by several groups (10–13), including our own, in the validation of many diagnostic tests for DVT.

Blood for D-dimer testing was drawn at enrollment, and the SimpliRED assay was performed within 1 hour of collection by trained laboratory technicians who were blinded to the clinical status of the patient and the results of other diagnostic testing for DVT. Because structured clinical prediction rules have not been validated in pregnancy (21), we categorized the pretest probability of each patient as low, intermediate, or high on the basis of the clinician's earlier impression. These assessments were performed by experienced clinicians before the results of other diagnostic tests were known. All patients recruited into the study were advised to return on an emergency basis if clinical symptoms consistent with DVT or PE developed. Such patients were then investigated with appropriate diagnostic testing consistent with the local center's usual practice.

Statistical Analysis

Patients were categorized as DVT positive if the results of their diagnostic compression ultrasonography at presentation were positive or if they had symptomatic DVT or PE on follow-up. Patients with negative ultrasonography results at presentation and no VTE in follow-up were categorized as DVT negative.

The test characteristics (sensitivity, specificity, and negative predictive value) and likelihood ratios of the SimpliRED assay and their corresponding 95% CIs were calculated on the basis of the D-dimer test result at the time of initial presentation and the presence or absence of diagnosed DVT in the patient over the duration of the study.

Role of the Funding Sources

Partial funding was provided over 2 years by the Heart and Stroke Foundation of Ontario (grant NA 5048) to recruit patients into the study. The SimpliRED assay kits were provided by Agen Biomedical, Brisbane, Australia. The company had no role in the design or conduct of the study or the decision to submit the paper for publication.

RESULTS

A total of 149 pregnant women were enrolled over the study period. Suspicion for DVT in these patients was almost always triggered by 1 or more of the following symptoms: unilateral leg swelling, pain in the leg, and discoloration of the leg. Each patient was referred from the emergency department or their primary practitioners. A total of 55, 40, 12, 36, and 6 patients were recruited, respectively, from centers 1, 2, 3, 4, and 5. **Table 1** shows patient characteristics. About half of the women were 35 years of age or older, 78.5% were white, and 50% had had

1 or more children before the index pregnancy. Although most patients had singleton pregnancies (89.3%), a high proportion of pregnancies were multiple—10.7%, compared with the national average of 2.7% (23). One reason for this may be that center 1 specializes in multiple pregnancies, and that center contributed about one third of the patients. Another reason may be that women with multiple pregnancies frequently report nonthrombotic leg symptoms. Most of the women presented for investigation in their third trimester, and most reported symptoms in the left leg (**Table 1**).

Twelve cases of DVT were diagnosed on the basis of the initial compression ultrasonography results, and 1 patient developed PE within 2 months of follow-up. Therefore, the overall prevalence of VTE in our cohort was 8.7% (13 of 149). Two of the 16 patients with multiple pregnancies (12.5%) had DVT, compared with 11 of the 133 patients with singleton pregnancies (8.3%). The prevalence of thromboembolic events was similar across the centers (9% [5 of 55 patients] center 1, 5% [2 of 40] at center 2, 14% [5 of 36] at center 3, 8% [1 of 12] at center 4, and 17% [1 of 6] at center 5), and it did not significantly differ between patients with singleton and those with multiple gestations (13% [2 of 16 patients] vs. 9% [12 of 133 patients]; $P > 0.05$, Fisher exact test).

Eleven cases of DVT presented in the left leg and 1 presented in the right leg. Four cases of DVT were diagnosed in each trimester. The patient who developed PE did so 3 days after a second-trimester pregnancy loss, 55 days after her initial presentation with suspected DVT.

Table 1. Characteristics of Pregnant Women Presenting with Suspected Deep Venous Thrombosis

Characteristic	Patients, n (%)
Age	
<35 y	75 (50.3)
≥35 y	74 (49.7)
Race	
White	117 (78.5)
Black	4 (2.7)
Asian/Pacific Islander	12 (8.1)
Mixed	3 (2.0)
Other	12 (8.1)
Parity	
Nulliparous	74 (49.7)
≥1	75 (50.3)
Order of gestation	
Singleton	133 (89.3)
Twins/triplets	16 (10.7)
Stage of gestation at presentation	
<12 wk	8 (5.4)
12–28 wk	54 (36.2)
>28 wk	87 (58.4)
Symptomatic leg	
Left	67 (45.0)
Right	57 (38.3)
Bilateral	25 (16.8)

The sensitivity of the SimpliRED assay for the diagnosis of DVT in pregnancy is 100% (CI, 77% to 100% [13 of 13 patients]), the specificity is 60% (CI, 52% to 68% [81 of 135]), and the negative predictive value is 100% (CI, 95% to 100% [81 of 81]). Likelihood ratios for DVT were 2.5 (CI, 2.0 to 3.1) with a positive result on the SimpliRED assay and 0 (CI, 0 to 0.9) with a negative result. The likelihood ratios for DVT were 0.3 (CI, 0.1 to 0.8) with low pretest probability and 3.1 (CI, 2.1 to 4.8) with nonlow pretest probability (Table 2).

When we stratified the results of D-dimer testing by the presence or absence of patient risk factors, patients presenting in the first trimester of pregnancy with positive D-dimer results had a high prevalence of DVT (62.5%), regardless of whether these risk factors were present. Risk factors included family history of DVT, known acquired or inherited thrombophilia, prolonged bed rest or paralysis, active cancer, recent surgery, and use of fertility agents.

In the remaining 136 patients in whom DVT was not diagnosed, the SimpliRED assay result was equivocal in 1 patient, positive in 53 patients (39%), and negative in the remaining patients (60.1%). Among pregnant patients in whom DVT was not diagnosed, the SimpliRED assay results were positive in 0% in the first trimester, 24% in the second, and 51% in the third. This observation is consistent with findings from our pilot study (17). Medical conditions that could contribute to a false-positive SimpliRED assay result were reported in 23 patients; 4 patients had more than 1 condition. The SimpliRED assay result was positive in about 50% of these patients, who formed less than 16% of our cohort (Table 3).

DISCUSSION

The SimpliRED assay can be used to exclude DVT in pregnant women with suspicious symptoms because it is sensitive to the presence of disease in this cohort. Although other D-dimer tests have higher sensitivities for VTE in nonpregnant patients (96% to 100% vs. approximately 90%) (20), the SimpliRED assay also has reasonable spec-

ificity (60% in this study), and its results remain negative in most women without VTE. In contrast, all other assays (ELISA and latex microparticle assays) have very low specificities (<20%) and provide too many false-positive results to be useful (20, 21).

Despite the relatively small sample size, the wide CI on the observed 100% sensitivity of the SimpliRED assay, and the related wide CI on the likelihood ratio for a negative D-dimer test result (Table 2), we are confident about our results because the reported sensitivity of approximately 90% in several studies of nonpregnant patients suspected of having DVT and PE strengthens our findings (20). We can think of no biologically plausible mechanism whereby pregnant patients should have lower sensitivities; in fact, because D-dimer levels increase as pregnancy progresses, the sensitivity of the SimpliRED assay might increase with an expected decrease in specificity. Our study also shows that, not unexpectedly, the specificity of the assay decreases as pregnancy progresses, limiting its use in the latter part of the third trimester.

Because of its sensitivity, concerns have been raised about using the SimpliRED assay as a stand-alone test for all patients suspected of having DVT or PE (20). In particular, a normal result does not exclude the disease when the pretest probability for DVT or PE is high (20). Consequently, the SimpliRED assay should not be used as the initial diagnostic test in nonpregnant patients with suspected DVT or PE and a high pretest probability, because false-negative results are too common to reliably exclude the disease. Rather, the test can be used in conjunction with a pretest probability assessment, preferably by using a structured clinical prediction rule (20, 21). For example, the combination of a low pretest probability and a negative D-dimer test result excludes a diagnosis of either DVT or PE. Until further studies are done in pregnant women, we recommend this conservative approach; however, use of the clinician’s previous impression to assess pretest probability, in the absence of a validated, structured clinical pre-

Table 2. Performance of the SimpliRED Assay and Pretest Probability*

D-Dimer Test Result	PTP	Patients, n (%)	DVT Present, n (%)	DVT Absent, n (%)	Sensitivity (95% CI), % [n/n]	Specificity (95% CI), % [n/n]	Likelihood Ratio of DVT with Positive D-Dimer Result (95% CI)	Likelihood Ratio of DVT with Negative D-Dimer Result (95% CI)	Negative Predictive Value of D-Dimer Testing (95% CI), % [n/n]
Negative	Low	69 (44.6)	0 (0)	69 (46.6)	100 (77–100 [13/13])	60 (52–68 [81/135])	2.5 (2.0–3.1)	0 (0.0–0.9)	100 (95–100 [81/81])
	Nonlow†	12 (8.1)	0 (0)	12 (8.1)	–	–	–	–	–
Positive	Low	36 (24.3)	3 (2)	33 (22.3)	–	–	–	–	–
	Nonlow	31 (21)	10 (6.8)	21 (14.2)	–	–	–	–	–
Total		148 (100)‡	13 (8.8)	135 (91.2)	–	–	–	–	–

* Pretest probability is based on the clinician’s previous impression. The SimpliRED assay is manufactured by Agen Biomedical (Brisbane, Australia). DVT = deep venous thrombosis; PTP = pretest probability.
 † Includes intermediate and high pretest probability.
 ‡ Excludes 1 equivocal D-dimer test result.

Table 3. Frequency of Positive SimpliRED Assay Results in Pregnant Patients, by Trimester and Concurrent Medical Conditions*

Condition	Patients with Concurrent Medical Conditions, n	Positive SimpliRED Assay Result [95% CI], n (%)
Pregnancy	135†	53 (39 [31–48])
Stage of gestation		
<12 wk	3	0 (0 [0–60])
13–28 wk	51	12 (24 [14–37])
>28 wk	81	41 (51 [40–61])
Pregnancy complications‡	23	12 (52 [33–71])
Superficial phlebitis	9	2 (22 [7–56])
Other§	3	2 (66 [19–93])

* In the absence of deep venous thrombosis. The SimpliRED assay is manufactured by Agen Biomedical (Brisbane, Australia).

† Excludes 1 equivocal D-dimer test result.

‡ Includes hypertensive disorders, vaginal bleeding, active labor, ruptured membranes, infection, and liver disease.

§ Includes surgery, trauma, stroke, myocardial infarction, connective tissue disease, and cancer.

diction rule for pregnant women, added little clinical value in predicting DVT in the patients we studied.

A second concern with the SimpliRED assay is its subjectivity—it requires visual interpretation of the results, and inexperienced persons may misinterpret the findings. Because the assay can be performed on whole blood obtained by fingerstick at the bedside or on citrated or EDTA-containing blood taken from a vein into a test tube, we recommend that the test be performed only by laboratory personnel who have experience with interpretation of assay results (24).

Since D-dimer testing was introduced in the 1980s as a tool to aid in the diagnosis of VTE, many prospective studies have been performed to define its specific role; however, to our knowledge, ours is the first to prospectively evaluate any D-dimer assay for the diagnosis of DVT in pregnant patients (10–13). Our results, although preliminary, strongly suggest that the qualitative SimpliRED assay is specific enough to be useful for excluding DVT in pregnancy.

The greater potential of D-dimer testing in pregnant women may lie in the exclusion of PE. Currently, further objective testing to define the presence of venous thrombosis requires radiation; although such tests as spiral computed tomography, magnetic resonance imaging, and venography are considered safe (25, 26), they often cause duress to patients undergoing the tests. Because D-dimer testing is relatively noninvasive, does not use ionizing radiation, and does not harm the fetus, its role in pregnant women should be investigated and defined.

In conclusion, the SimpliRED assay appears to be sufficiently sensitive and specific to be clinically useful in pregnant women suspected of having DVT. A negative D-dimer test result appears to exclude DVT. The utility of this test is high for at least the first 2 trimesters of preg-

nancy. Its role in the diagnosis of PE in pregnant patients should be investigated further.

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