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Predicting Deep Venous Thrombosis in Pregnancy: Out in "LEFt" Field?

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Background: Clinicians' assessment of pretest probability, based on subjective criteria or prediction rules, is central to the diagnosis of deep venous thrombosis (DVT). Pretest probability assessment for DVT diagnosis has never been evaluated in pregnant women.

Objective: To evaluate the accuracy of clinicians' subjective assessment of pretest probability for DVT diagnosis and identify prediction variables that could be used for pretest probability assessment in pregnant women with suspected DVT.

Design: A cross-sectional study conducted over 7 years (March 2000 to April 2007).

Setting: 5 university-affiliated, tertiary care centers in Canada.

Patients: 194 unselected pregnant women with suspected first DVT.

Intervention: Diagnosis of DVT was established with abnormal compression ultrasonography at presentation or on serial imaging. Pretest probability by subjective assessment was recorded by thrombosis experts for each patient before knowledge of results.

Measurements: The sensitivity, specificity, negative predictive value, and likelihood ratios of subjective pretest probability assessment and their corresponding 95% CIs were calculated on the basis of the diagnosis of DVT. Patients were DVT positive if they had diagnostic compression ultrasonography at initial or serial testing or symptomatic venous thromboembolism on follow-up. Patients were DVT negative if they had negative compression ultrasonography at presentation and no venous thromboembolism on follow-up. A prediction rule for assessing DVT was derived, and an internal validation study was done to explore its performance.

Results: The prevalence of DVT was 8.8%. Clinicians' subjective assessment of pretest probability categorized patients into 2 groups: low pretest probability (two thirds of patients) with a low prevalence of DVT (1.5% [95% CI, 0.4% to 5.4%]) and a negative predictive value of 98.5% (CI, 94.6% to 99.6%), and nonlow pretest probability with a higher prevalence of DVT (24.6% [CI, 15.5% to 36.7%]). Three variables (symptoms in the left leg [L], calf circumference difference ≥2 cm [E], and first trimester presentation [Ft]) were highly predictive of DVT in pregnant patients.

Limitations: Few outcomes occurred. Altogether, 17 events were diagnosed during the study. The prediction rule derived should be validated on an independent sample before applying it to clinical practice.

Conclusion: Subjective assessment of pretest probability seems to exclude DVT when the pretest probability is low. Moreover, 3 objective variables ("LEFt") may improve the accuracy of the diagnosis of DVT in pregnancy. Prospective validation studies are needed.

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Although clinical assessment of deep venous thrombosis (DVT), based on risk factors and physical signs, can not be used alone to safely exclude or diagnose DVT (1, 2), clinical assessment of DVT using a combination of risk factors and physical signs plays an important role in current diagnostic strategies of DVT in the general population (3–6).

In the past decade, many strategies, using D-dimer testing and clinical assessment in combination with compression ultrasonography, for the diagnosis of DVT in the general population have been published (3–6). The use of clinicians' assessment for pretest probability on the basis of a structured prediction rule (7) in combination with D-dimer testing and compression ultrasonography can effectively exclude the presence of DVT at initial presentation and identify patients who require further evaluation with repeated compression ultrasonography or contrast venography (3–6).

For many reasons, pregnant women have not been included in these studies. Although pregnancy is recognized as a risk factor for venous thrombosis (8–10), no prospective studies validate the use of current diagnostic strategies for DVT. In addition to the fact that the most often used prediction rule (the Wells clinical prediction model [7]) was not derived by using pregnant patients, the difficulty with adopting this prediction rule and applying it directly to pregnant patients is the degree to which many of the comorbid conditions, which are risk factors for DVT (such as cancer and recent surgery), are absent in the younger, healthier cohort of pregnant women. The Wells prediction rule has been less sensitive for an ambulatory population with a low prevalence of DVT (11). Moreover, nonthrombotic leg symptoms (swelling and pain)

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Context

The clinical predictors of deep venous thrombosis (DVT) are well known in the general population but not in pregnant women.

Contribution

In 7 years, 5 centers enrolled 194 pregnant women with suspected DVT. Clinical thrombosis experts evaluated the women and did leg vein compression ultrasonography. Seventeen (8.8%) women had DVT. Clinical predictors of DVT were left leg symptoms, difference in calf circumference of 2 cm or more, and presentation during the first trimester of pregnancy. All 17 women with DVT had at least 1 of these predictors.

Caution

Too few women had DVT to independently validate the findings.

Implication

Presentation during the first trimester of pregnancy and a symptomatic left leg should raise suspicion of DVT in pregnancy.

—The Editors

are common in pregnancy and can be indistinguishable from those seen in patients with DVT.

In the absence of a validated prediction rule, the diagnosis of DVT in pregnant patients relies heavily on the use of compression ultrasonography (12). In a pooled analysis of studies investigating its test characteristics in the general population, compression ultrasonography is highly sensitive (97% [95% CI, 96% to 98%]) and specific (94% [CI, 90% to 98%]) for detecting symptomatic proximal DVTs (13). However, similar data do not exist for pregnant patients. Because the sensitivity of single compression ultrasonography at the time of presentation in a pregnant patient is unknown, serial testing with compression ultrasonography over 7 days or further invasive testing (leg venography) or other diagnostic testing (for example, magnetic resonance imaging) in these patients is recommended. Similarly, no data on the accuracy of clinicians' subjective assessment of pretest probability in these patients are available.

In this study, we evaluated how well clinicians' subjective assessment of pretest probability identifies the presence or absence of DVT in symptomatic pregnant patients. In addition, we sought to identify variables in this specific cohort of patients that might be used to accurately assess pretest probability of DVT.

METHOD

Study Strategy

We recruited pregnant women who presented in participating centers. By using compression ultrasonography with clinical follow-up, we determined the presence or absence of DVT in these patients. In a cross-sectional analysis, we assessed the accuracy of clinicians' assessment of pretest probability, as well as objective variables in determining the presence or absence of DVT in these patients.

Study Sample

Unselected pregnant women who presented to 1 of 5 Canadian centers (Women's College Hospital, Toronto; Hamilton Health Sciences Corporation, McMaster University Medical Centre, Henderson Hospital, and St. Joseph's Healthcare Centre, Hamilton; and Ottawa Hospital Civic and General Campuses, Ottawa, Ontario) from March 2000 to April 2007 with suspected DVT were potentially eligible for the study. The Hamilton and Ottawa centers are tertiary referral sites for thrombosis; the Toronto, McMaster, St. Joseph's, and Ottawa sites are tertiary referral centers for pregnant women. The study investigators from these sites have previously collaborated in other venous thromboembolism diagnostic studies in nonpregnant patients and are currently involved and are collaborating in other related long-term pregnancy studies. The level of commitment to perform and complete this specific study remained high over these 8 years.

We excluded patients who had a history of venous thromboembolism, had concomitant symptoms consistent with pulmonary embolism, were unable or unwilling to return for follow-up, were geographically inaccessible, or did not provide consent or receive consent from the attending physician.

Study Flow

The institutional research boards of all participating centers reviewed and approved the protocol. The physicians who initially assessed potential study participants were emergency physicians, obstetricians, and general internists. On the basis of their clinical assessments, these physicians were suspicious of DVT and consulted thrombosis experts who obtained informed consent from the patient for study participation. After obtaining informed consent, the experts examined the patient; assessed the pretest probability (based on subjective criteria), categorized as low, moderate, or high; and documented the presence of each variable of interest. They did these assessments before testing with compression ultrasonography. They did not filter patients to omit compression ultrasonography on any study patient.

Eleven variables that could be used to identify the presence of DVT included 5 of those described in the Wells model (7) and 6 other variables, including the presence of varicosities, peripheral pulses, redness, warmth, trimester of presentation, and side of symptomatic leg. Investigators' consensus determined whether these latter variables were present. Components of the Wells clinical prediction model selected for our study included calf tenderness, pitting edema of the symptomatic leg, presence of any risk factors (cancer or paralysis, as well as such

pregnancy-specific factors as the use of assisted reproductive techniques), difference in calf circumference between asymptomatic and symptomatic legs (2 cm), and presence of an alternate diagnosis more likely than DVT (7). The experts who collected the variables were all aware of the Wells model but knew that it had been derived in a sample that did not include pregnant patients and that they could not apply the rule to the current study cohort.

All patients had compression ultrasonography of the symptomatic leg or legs after assessment by the thrombosis expert. Ultrasonography was done with compression of the deep veins of the legs along the entire length of the proximal veins, including the common femoral, superficial femoral, popliteal, and calf trifurcation. If the examiner suspected isolated iliac venous thrombosis, the iliac vein was visualized by direct imaging and Doppler flow. If the initial compression ultrasonography result was negative, some patients had repeated compression ultrasonography on days 3 and 7, according to the clinician's standard of practice. Deep venous thrombosis was diagnosed when a venous segment was noncompressible and, for the iliac veins, by the absence of flow within the iliac vein or the presence of a visible iliac thrombus by B-mode imaging. All patients with DVT received unfractionated or low-molecular-weight heparin.

All patients who had normal compression ultrasonography results after initial testing had anticoagulants withheld and received clinical follow-up for at least 3 months to ensure the correctness of the initial assessment that DVT was not present. These patients were seen at least once during follow-up and were contacted by telephone at the end of 3 months. If clinical symptoms consistent with DVT or pulmonary embolism developed, the patients had diagnostic testing consistent with the local center's usual practice.

Statistical Analysis

We described the characteristics of the study sample as means and proportions. We defined patients as DVT positive if they had diagnostic compression ultrasonography at initial or serial testing or symptomatic DVT or pulmonary embolism in follow-up. We categorized patients with negative compression ultrasonography at presentation and no venous thromboembolic event in follow-up as DVT negative. We calculated the test characteristics (sensitivity, specificity, and negative predictive value [defined as the proportion of patients with a negative result who do not have the disease—in this case, DVT]) of clinicians' subjective pretest probability (low or nonlow pretest probability) and their corresponding 95% CIs by using compression ultrasonography as the diagnostic reference standard for DVT.

We initially did univariate analysis on all of the 11 selected variables that could potentially predict DVT. We entered variables that were significantly associated with presence of DVT at a P value of 0.05 or less into a multivariate model to identify independent risk factors for DVT. We entered variables 1 at a time, retaining only those that increased the c-statistic for the model by at least 0.03. We then used the final multivariate model to propose a prediction rule. If a patient displayed none of the characteristics chosen as significant in the multivariate model selection process, the proposed prediction rule classified that patient as having a low probability of DVT. We therefore divided the patients into 2 groups: low pretest probability and nonlow pretest probability.

A problem with deriving clinical prediction rules is that they always do better in the sample used to derive them than in independent validation samples. One reason for this is that even if the sample population accurately represents the target population, the derivation of a prediction rule typically involves considering many potential predictor variables. A common rule of thumb for multivariate logistic regression is that for the parameter estimates to be stable, at least 5 to 10 events per independent variable should be in the model (14). Our data contain 17 DVT events. Although our final rule only uses 3 variables, we derived the rule by using an initial model with 6 independent variables.

To assess whether the formal validation study we plan to do will find our rule useful, we conducted an internal, bootstrap-based validation analysis in which we randomly selected three quarters of our patients ($n = 146$). We then used the same procedure to derive a rule for those patients and applied the resulting rule to the remaining patients ($n = 48$). To be specific, we applied the same forward selection model-building procedure on the basis of the c-statistic to derive a logistic regression model for the random subsample. We defined the resulting prediction rule as categorizing a patient as having low pretest probability of DVT if the patient had none of the variables chosen as significant in the model. Because we only used 75% of our actual sample to derive the rule, we could independently assess the performance (sensitivity, specificity, and negative predictive value) of the rule on the remaining 25% of the sample.

For the internal validation analysis, we repeated this procedure 1000 times and summarized the results. By simulating what would happen if we had derived our rule on an initial sample and then validated it on a further independent sample, we could explore how often the same predictor variables would be chosen by using different data sets and assess the procedure used to derive our rule. In particular, we wanted to verify that this procedure typically leads to a rule that does well on an independent validation set. Summarizing the true performance (sensitivity, specificity, and negative predictive value) of 1000 different rules derived using the same procedure more honestly characterizes the probable performance of such a rule than simply describing how the "LEFt" rule (symptoms in the left leg [L], calf circumference difference $\geq$2 cm between asymptomatic and symptomatic legs [E], and

Table 1. **Characteristics of Pregnant Patients Who Presented With Suspected Deep Venous Thrombosis**

Characteristic	Patients, *n* (%)
Age	
<35 y	139 (71.6)
≥35 y	55 (28.4)
Pregnancy	
Singleton	176 (90.7)
Twins or triplets	18 (9.3)
Parity	
Nulliparous	88 (45.4)
≥1	106 (54.6)
Gestational age at investigation	
≤12 wk	9 (4.6)
>12 to 28 wk	74 (38.1)
>28 wk	111 (57.2)
Symptomatic leg	
Left	90 (46.4)
Right	75 (38.7)
Bilateral	29 (14.9)

first trimester presentation [Ft]) performs on its derivation data set. In other words, because we did not measure the performance on the same data that we used to derive the rule, we would not exaggerate performance quality by overfitting.

We used the statistical software package SAS, version 9.1 (SAS Institute, Cary, North Carolina). Statistical significance was defined as a 2-sided α level of 0.05 for comparison of proportions. We did the validation analysis with the open source statistical software R (www.r-project.org).

Role of the Funding Source

The Heart and Stroke Foundation of Ontario provided partial funding to recruit half of the patients in the cohort. The funding source had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

We recruited 194 pregnant women with suspected DVT over 8 years. Among 182 patients who did not receive a diagnosis of DVT on initial negative compression ultrasonography, 152 patients had serial testing and 4 patients subsequently received a diagnosis of DVT. One patient received a further diagnosis of DVT during the 3-month follow-up. Therefore, a total of 17 patients (8.8%) received a diagnosis of DVT. **Table 1** shows the characteristics of all recruited patients. Most patients were younger than 35 years (71.6%), had singleton pregnancies (90.7%), and had 1 (or more) previous delivery (54.6%). Most women presented in the third trimester (57.2%). The distribution of DVT diagnosed by trimester was 5 cases (29.4%) in the first trimester, 6 cases (35.3%) in the second trimester, and 6 cases (35.3%) in the third trimester. Patients most often had symptoms in 1 leg: left (46.4%) or right (38.7%).

Table 2 shows the results of univariate analysis with all 11 variables on our full data set. Six variables were significant predictors for DVT: symptomatic left leg ($P = 0.003$), calf circumference difference of 2 cm or more ($P < 0.001$), first trimester of presentation ($P < 0.001$), alternate diagnosis ($P = 0.012$), redness ($P = 0.03$), and warmth ($P = 0.008$). We entered these variables into our forward regression model 1 at a time, starting with the most predictive variables (calf circumference difference, first trimester of presentation, and left leg symptoms) and then the weaker ones (alternate diagnosis, redness, and warmth). The c-statistic (a measure of the probability that a person with the target condition will have a higher score from the model than a person without the target condition), associated with the model containing the 3 most significant variables (calf circumference difference, first trimester of presentation, and left leg symptoms), was 0.943. The c-statistic did not increase substantially (<0.03) with the addition of the other remaining 3 variables (alternate diagnosis, redness, and warmth) to the model (c-statistic,

Table 2. **Results of Univariate Analysis of Potential Predictive Variables for DVT in Pregnant Patients***

Variable	Patients, *n/n*	Patients With Variable When DVT Is Present, *n*	Unadjusted OR for DVT (95% CI)	*P* Value
Symptomatic left leg	90/194	16	22.27 (2.89–171.65)	0.003†
Alternate diagnosis	96/194	3	0.19 (0.05–0.70)	0.012†
Pulses present	174/185	15	0.42 (0.09–2.15)	0.30
Pitting edema	84/193	11	2.59 (0.92–7.31)	0.07
Redness	47/193	8	3.12 (1.13–8.63)	0.03†
Warmth	48/194	9	3.98 (0.26–18.21)	0.008†
Risk factors present‡	60/194	3	0.45 (0.13–1.63)	0.23
Varicose veins	44/193	1	0.19 (0.03–1.50)	0.12
≥2-cm calf circumference difference	25/148	11	13.62 (4.56–40.67)	<0.001†
First trimester	9/194	5	18.02 (4.27–75.99)	<0.001†
Tenderness along vein	92/193	11	2.15 (0.76–6.07)	0.15

DVT = deep venous thrombosis; OR = odds ratio.
* Observations with missing data points were excluded from the analysis.
† Significant predictive variables: $P < 0.05$.
‡ Risk factors include cancer, trauma, family history, use of assisted reproductive techniques, known thrombophilia, and prolonged bedrest.

0.959). **Table 3** shows the multivariate analysis describing the 3 variables and the corresponding odds ratio.

Table 4 shows the accuracy of thrombosis expert clinicians' subjective assessment of pretest probability for the presence of DVT based on presentation and physical examination. The expert clinicians assessed most patients (67.5%) as having a low pretest probability for DVT. The remaining 62 patients (32.5%) had either a moderate or high (nonlow) pretest probability for DVT. In the patients with low pretest probability, the prevalence of DVT in 2 of 131 patients was 1.5% (CI, 0.4% to 5.4%). Among those with nonlow (moderate or high) pretest probability, the prevalence of DVT in 15 of 61 patients was 24.6% (CI, 15.5% to 36.7%; $P < 0.001$, for comparison of prevalences of DVT in the 2 subgroups). The likelihood ratio (defined as the proportional change in the odds of disease after a test result, which is equivalent to the ratio of posttest odds to pretest odds) associated with a low pretest probability was 0.16 (CI, 0.04 to 0.59), and the likelihood ratio for a nonlow pretest probability was 3.4 (CI, 2.5 to 4.5). The likelihood ratio associated with a high pretest probability was 12.9 (CI, 5.9 to 28.2). The negative predictive value of a low pretest probability was 98.5% (CI, 94.6% to 99.6%).

Table 4 also summarizes the performance of the 1000 bootstrap prediction rules. When we assessed the sensitivity of the bootstrap rule (low pretest probability defined by having no model-selected variables), the median sensitivity was 100%. We also found that 95% of the rules had sensitivities from 50% to 100%. Thus, although our rule-derivation procedure produced a rule with perfect sensitivity at least 50% of the time, the sensitivity could also be rather poor. The median likelihood ratio associated with having none of the variables selected by the model-fitting procedure was 0. The likelihood ratio associated with a negative test result represents the amount by which the previous odds of DVT are multiplied when the test result is negative. A likelihood ratio of 0 indicates a perfect test in that no matter how likely one might think a given patient has DVT, a negative test result reduces the odds of DVT to 0. The 95% bootstrap interval extends up to 0.8, which means that a likelihood ratio of 0.8 is plausible. The wide confidence range indicates that the rule should be validated in a separate study before its application to clinical practice, because a likelihood ratio of 0.8 indicates that a negative result would only decrease the previous odds of DVT by 20%.

Table 5 shows the frequency with which the 3 most predictive variables (calf circumference difference, first trimester of presentation, and left leg symptoms) were present among pregnant women with suspected DVT and the corresponding prevalence of DVT associated with each variable. In 46% of patients who had a symptomatic left leg, the prevalence of DVT was 17 times higher than that in women who had symptoms in either the right leg or both legs. For women who presented with symptoms in the first trimester, DVT was diagnosed 8 times more often than any other trimester. Similarly, women with calf circumference difference of at least 2 cm were 18 times more likely to receive a diagnosis of DVT. Among the patients who had DVT, all had at least 1 LEFt variable, and at least 82.4% (14 of 17 patients) had 2 variables. Among patients who did not receive a diagnosis of DVT, half of the patients had none of the LEFt variables (50.3% [88 of 175 patients]) and 10 (5.7%) had 2 or more variables. When a pregnant patient with suspected DVT presented with none of these 3 variables, DVT was never diagnosed (0% [CI, 0% to 4.2%]). When 1 or more variables were present, DVT was diagnosed in 16.4% of cases (CI, 10.5% to 24.7%). With 2 or 3 variables (only 1 patient had all 3 variables), DVT was diagnosed in 58.3% of cases (CI, 35.8% to 75.5%).

Table 3. **Results of the Multivariate Analysis of Potential Predictive Variables for Deep Venous Thrombosis in Pregnant Patients**

Variable	Adjusted Odds Ratio (95% CI)	*P* Value
Symptomatic left leg	44.28 (3.22–609.69)	0.005*
≥2-cm calf circumference difference	26.89 (6.10–118.54)	<0.001*
First trimester	53.43 (7.12–401.02)	0.001*

* Significant predictive variables: $P < 0.05$.

Discussion

We searched MEDLINE and the ClinicalTrials.gov registry for relevant studies that reported the assessment of pretest probability or diagnosis of DVT in pregnant women up to June 2008; the search yielded no relevant studies.

Clinicians who are experts in subjective assessment of pretest probability of thrombosis categorize pregnant women who present with suspected DVT into 2 distinct groups: low pretest probability (comprising about two thirds of patients) with a low prevalence of DVT (1.5%) and nonlow pretest probability (comprising the remaining one third) with a higher prevalence of DVT (24.6%). In addition, we identified 3 easy-to-determine clinical variables that can be used to help less-experienced clinicians delineate the likelihood of DVT in pregnant patients. These 3 variables—symptomatic leg at presentation, calf circumference difference of 2 cm or more, and first trimester of presentation—can be used to categorize pregnant women who have none or 1 variable as unlikely to have DVT and those with 2 or 3 variables as likely to have DVT. Our findings are important because clinicians' pretest assessment (based on prediction rule) plays an important role in diagnostic algorithms of DVT in the general population and is used to enhance the accuracy of compression ultrasonography (3–6). To date, however, use of pretest assess-

Table 4. **Subjective Pretest Probability Assessment and Performance of the LEFt Variables in Predicting DVT in Pregnant Patients***

Variable	DVT Present, *n*	DVT Absent, *n*	Sensitivity (95% CI), %	Specificity (95% CI), %	NPV (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)
Pretest probability assessment							
Low	2	129	88 (62–98)	74 (66–80)	98.5 (95–100)	3.4 (2.5–4.5)	0.16 (0.04–0.59)
Moderate or high	15	46	–	–	–	–	–
Low or moderate	7	167	59 (36–78)	95 (91–98)	96.0 (92–98)	12.9 (5.9–28.2)	0.43 (0.24–0.76)
High	10	8	–	–	–	–	–
LEFt variables							
0	0	89	100 (81–100)	50 (43–58)	100 (96–100)	2.0 (1.7–2.3)	0 (0–0)
≥1	17	88	–	–	–	–	–

DVT = deep venous thrombosis; LEFt = left leg symptoms (L) and ≥2-cm calf circumference difference (E) presented in the first trimester (Ft); LR = likelihood ratio; NPV = negative predictive value.
* Observations with missing data points were excluded from the analysis.

ment in pregnant patients with suspected DVT has never been studied. Our study demonstrates that thrombosis specialists can accurately characterize the pretest probability of DVT in pregnant women with suspected DVT. It also suggests that a simple rule based on 3 objective, reproducible, and easily measured variables may also perform well.

Our study has certain limitations, the most important of which is the small number of DVT events used for the analysis. With this small number, the strength of additional variables, such as presence of an alternate diagnosis and presence of tenderness that could be predictive of DVT in pregnant women, cannot be thoroughly tested. This small number of DVTs reflects the fact that the prevalence of DVT in pregnant women who present with suspicious symptoms is low because pregnant women are younger and have fewer comorbid conditions. In addition, nonthrombotic symptoms, such as leg swelling, is common. In performing our study, we also excluded pregnant women with previous venous thromboembolic disease because of the difficulty associated with diagnosing recurrent DVT by using venous ultrasonography in participants with previous disease. These women would have an increased risk for recurrent DVT (10, 15). The low prevalence of DVT within our cohort (<10%) and the low incidence of comorbid conditions reported by the pregnant patients also limited our ability to measure the effect of other risk factors, such as cancer, trauma, or fractures, on DVT risks. These comorbid conditions and risk factors, if present, would increase the risk for DVT.

Table 5. **Frequency and Prevalence of DVT for the LEFt Variables**

Variable Present	Frequency of Variable, *n* (%)	Prevalence of DVT (95% CI)	*P* Value*
Symptomatic leg			
Left leg	90 (46.4)	17.8 (11.3–27.0)	<0.001
Bilateral or right leg	104 (53.6)	1.0 (0.1–5.2)	
Calf circumference difference			
≥2 cm	25 (16.9)	44.0 (26.6–63.1)	<0.001
<2 cm	123 (83.1)	2.4 (0.9–6.9)	
Trimester			
First	9 (4.6)	55.6 (26.2–81.3)	<0.001
Second or third	185 (95.4)	6.5 (3.8–11.0)	
LEFt variables			
0 or ≥1			
0	88 (45.8)	0 (0–4.2)	<0.001
≥1	105 (54.2)	16.4 (10.5–24.6)	
≤1 or >1			
≤1	158 (86.8)	0.6 (0.1–3.5)	<0.001
>1	25 (13.2)	58.3 (35.8–75.5)	
Overall	194 (100)	8.8 (5.5–13.6)	

DVT = deep venous thrombosis; LEFt = left leg symptoms (L) and ≥2-cm calf circumference difference (E) presented in the first trimester (Ft).
* The *P* value reflects the significant difference between the 2 variables used for comparison.

In addition to these limitations, the experts who evaluated pretest probability of DVTs in these patients are familiar with the Wells rule for nonpregnant patients because some of them participated in the key studies in deriving this rule. This rule may have influenced the expert's assignment of pretest probability in this study. However, each participating expert knew that the Wells rule was not derived from pregnant patients and that the presentation of DVT in pregnant patients could differ from that in nonpregnant patients. Hence, from the start of the study, these experts were encouraged to use "subjective" assessment alone in determining the pretest probability in these patients.

A further limitation to this study is the selection of our reference standard for DVT, which was a composite outcome of serial testing and clinical follow-up. The ideal study to classify patients as DVT positive or DVT negative is one in which every patient has contrast venography—the gold standard. For ethical reasons, venography cannot be done routinely in all pregnant patients. In addition, the composite outcome that we used has become the standard in many other DVT diagnostic studies in nonpregnant women (16–18), and we believe that although this approach is not "validated" in pregnant women, it is a sensible choice. Related limitations are the failure to do serial compression ultrasonography in all pregnant women. A

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DVT could have been "missed" with a single ultrasonography, but missing it entirely is highly unlikely because all patients in the study were followed clinically for 3 months after presentation. A missed event is unlikely to remain asymptomatic. In the vast majority of patients (83.5%), serial testing with compression ultrasonography was, in fact, done.

In this study, we developed a prediction rule that could be used to assess for the presence of DVT in pregnant women. Before the application of a prediction rule to clinical practice, one must validate it with an independent study. Our internal validation study suggests that the prediction rule may do well in an independent validation study (**Table 4**). However, the CIs for the measures of rule performance are quite wide, which means that we cannot be certain of the rule performance in an independent validation set.

For the purpose of this study, we arbitrarily used a cut-off of 2 cm instead of 3 cm for calf circumference difference (as described in the Wells model [7]), because we wanted to improve the sensitivity of the variable and to miss as few events as possible. This variable, in our analysis, was in fact the most predictive of DVT in pregnant patients. Patients who present with symptoms suspicious of DVT in the early trimester of pregnancy are more likely to receive a diagnosis of DVT than those who present with suspicious symptoms in the later trimesters (second or third) because nonthrombotic causes of leg swelling are more common in late trimesters. The incidence of DVT in all 3 trimesters, however, is similar (5 events in the first trimester and 6 events in the second and third trimesters) to a previous study (19). The more frequent involvement of the left leg in DVT in pregnant women is not a novel finding. In a pooled analysis of observational studies of DVT in pregnancy, left leg only or both legs were more commonly involved (82.2% [CI, 75.1% to 87.5%]) compared with right leg only (19). In our study, 46.4% of patients ($n = 194$) with suspected DVT reported left leg symptoms only; patients who reported left leg symptoms only presented with 94% (16 of 17 patients) of all episodes of DVT.

To our knowledge, our study is the first of its kind to evaluate the performance of clinicians' subjective assessment of pretest probability in pregnant women who present with suspected DVT. Although subjective assessment of pretest probability by thrombosis experts in pregnant women seems sensitive in identifying pregnant women with DVT, the use of "gestalt" is likely to be less accurate when used by clinicians who are less experienced at evaluating suspected DVT (20). The 3 easy-to-determine variables would simplify assessment of pretest probability in pregnant women and is easily remembered as the acronym LEFt: left leg (L), calf circumference difference of at least 2 cm (E), and first trimester presentation of symptoms (Ft). If none of the 3 variables are present, DVT is unlikely; conversely, the presence of 1 or more of these variables increases the probability of DVT substantially. Applying the LEFt variables should enhance the accuracy of a subsequent single or serial compression ultrasonography and effect on the clinician's ability to diagnose DVT in pregnant women.

Clinicians' subjective assessment of pregnant women with suspected DVT is useful because a very low pretest probability means that DVT is very unlikely. When the pretest probability is not low, the prevalence of DVT is sufficiently high to merit further diagnostic testing. Three easy-to-determine variables (symptomatic left leg, difference in calf circumference $\geq$2 cm, and first trimester of presentation) are useful in evaluating pretest probability. If prospective studies validate these findings, they can assist clinicians in the assessment of DVT before objective testing.

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