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ORIGINAL ARTICLE

Excluding pregnancy-associated deep vein thrombosis with whole-leg ultrasound

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Abstract

Background: Deep vein thrombosis (DVT) is common in pregnancy, yet data are limited on the best diagnostic strategies in pregnant patients suspected of DVT.

Objectives: We conducted a prospective cohort study to evaluate the rate of symptomatic DVT in the 90 days after a negative whole-leg compression ultrasound (CUS) in pregnant women presenting with DVT symptoms.

Methods: In this prospective cohort study, we enrolled pregnant patients suspected of DVT between 2011 and 2019 who were referred to the vascular imaging laboratory at a tertiary care center and had anticoagulation held after a negative whole-leg CUS. Primary outcome was objectively confirmed DVT or pulmonary embolism or death due to venous thromboembolism (VTE).

Results: Whole-leg CUS yielded normal results in 186 patients (97.9%) and identified DVT in 4 (2.1%). The mean age was 30 and 164 were White. Among the 186 patients with a negative, initial whole-leg CUS who did not receive anticoagulation, there were 2 DVT events identified over the 90-day follow-up period, for an overall rate of 1.1% (95% CI: 0.2-3.4%). The study was terminated before full planned accrual for administrative reasons.

Conclusion: The rate of symptomatic DVT is low in pregnant patients who have a single, negative whole-leg CUS and did not receive anticoagulation. Adequately powered studies should prospectively assess whole-leg CUS in a larger population alone and in combination with pre-test probability scores and/or D-dimer to determine its role in the evaluation of suspected DVT in pregnancy.

KEYWORDS
leg, pregnancy, prospective studies, thrombosis, venous thromboembolism

Essentials

- Diagnosis of deep vein thrombosis (DVT) in pregnancy remains challenging.
- Pregnant patients suspected of DVT with negative whole-leg compression ultrasound were followed for 90 days.
- The rate of DVT was low (1.1%), but the study was terminated early.
- Future studies should combine whole-leg compression ultrasound with pre-test probability scores or D-dimer.

1 | INTRODUCTION

Pregnancy and the postpartum period are well-established risk factors for deep vein thrombosis (DVT), which complicates 1 out of 1600 pregnancies [1–3]. DVT can occur in isolation and is associated with adverse obstetrical outcomes and maternal morbidity [1]. DVT can also lead to pulmonary embolism, the leading cause of maternal death in Western countries. Thus, accurate and prompt diagnosis in the pregnant patient is crucial.

Although many studies examining diagnostic strategies for DVT have been published, pregnant patients have predominantly been excluded [4]. Diagnosis of DVT in pregnancy is complicated by the overlap between physiological changes of pregnancy with symptoms of DVT, including leg swelling and pain, and laboratory findings, including a rise in D-dimer with each trimester [5]. Relatively little is known about the safest and most accurate means of DVT diagnosis in pregnancy.

Whole-leg compression ultrasound (CUS) is a diagnostic imaging modality that has been proven in large clinical trials to be highly accurate and efficient in the diagnosis of DVT in nonpregnant patients [6]. A recent systematic review and meta-analysis of whole-leg CUS revealed a very high accuracy, but only 57 pregnant patients were included [7]. In addition, a prospective study explored use of the novel LEFt clinical prediction rule (DVT symptoms in the left leg; calf circumference >2 cm larger in symptomatic leg; first trimester of pregnancy) to simplify the diagnosis of DVT in pregnancy, but further confirmation of its performance characteristics is needed prior to its widespread adoption [8–10].

We conducted a prospective study to evaluate the 90-day rate of DVT in pregnant patients suspected of DVT after a single, negative whole-leg CUS. We also calculated the elements of the LEFt clinical prediction rule to further explore its performance in this population.

2 | METHODS

2.1 | Patients

Between February 2011 and April 2019, we consecutively enrolled all pregnant patients referred to a tertiary care hospital for suspected, first episode of DVT during hours when research coordinators were available (generally weekdays and selected evenings). Women of childbearing age referred per standard clinical practice to the peripheral vascular laboratory (the institution's sole venue for vascular ultrasound) by obstetricians, obstetrical nurse-practitioners or certified nurse midwives, and family medicine physicians were identified by screening of the laboratory schedule daily by the research coordinator.

Due to the lack of specificity of D-dimer during pregnancy and in accordance with contemporary clinical practice guidelines at the time of study design, patients did not undergo initial screening with D-dimer testing [11]. Pregnant patients who provided informed consent underwent a focused history and physical examination by a clinician to verify study inclusion criteria and identify the components of the LEFt clinical prediction score. Exclusion criteria included previous DVT, technical inability to perform comprehensive duplex ultrasonography, anticipated inability to obtain long-term follow-up, inability to provide informed consent, current therapeutic anticoagulation, or planned use of long-term anticoagulation for another diagnosis. In all, 189 patients were deemed eligible and enrolled after screening (see cohort flow chart in Figure). A comprehensive screening log was not kept, due to the small proportion of pregnant patients in the screened population. However, any patient approached for enrollment who declined to provide consent was noted.

Following enrollment, patients underwent objective testing for DVT with a single whole-leg CUS of the symptomatic leg. Patients with a negative result on the whole-leg CUS did not receive anticoagulants and were instructed to contact their treating clinicians and study staff with new or progressive symptoms suggesting thrombosis. Patients found to have DVT on initial whole-leg CUS were excluded from follow-up and further analysis and managed by the treating physician (Figure).

The Intermountain Health Institutional Review Board approved the study, and all enrolled patients provided written informed consent. The protocol was registered with clinicaltrials.gov (NCT01319474).

2.2 | Objective testing for DVT

Whole-leg CUS was performed immediately after enrollment and assessment of the LEFt clinical prediction score. We used a modified version of the technique of Talbot, which has been described in detail [6,12]. A high-resolution, electronically focused linear array transducer with a 3.5- to 10-MHz variable frequency probe (model 5000 scanner, ATL Corp) was used for all studies. Registered vascular technologists performed all whole-leg CUS, and certified vascular surgeons on the hospital staff interpreted the results. Interpreting physicians were unaware of the enrollment clinicians' assessment and the LEFt score.

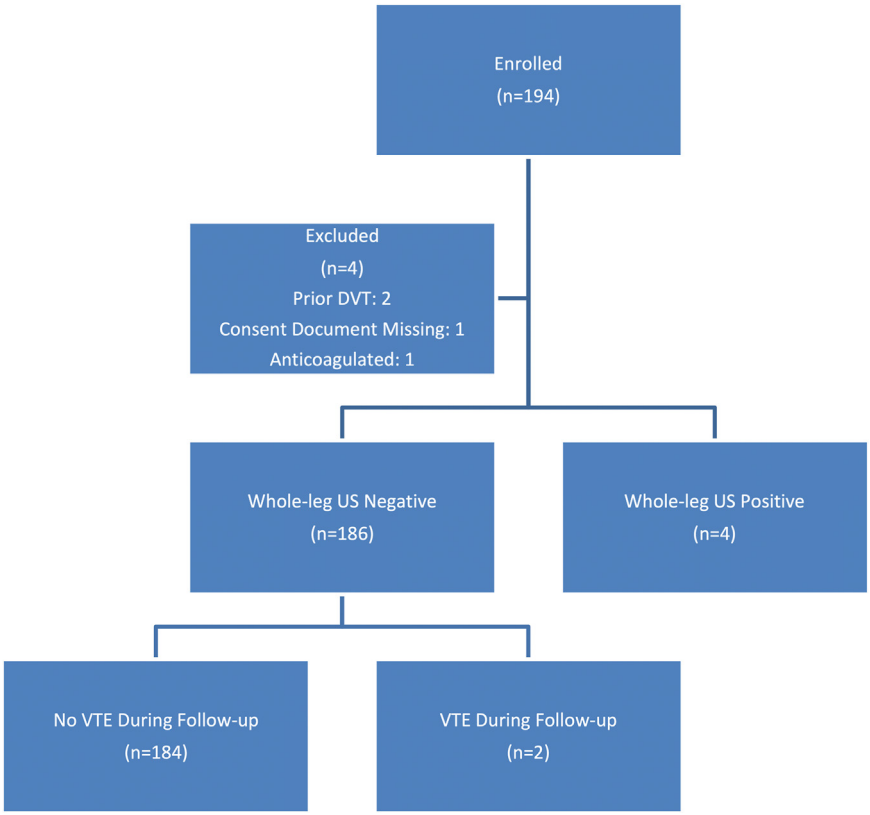
2.3 | The LEFt clinical prediction rule

For a secondary analysis, participating patients were evaluated to calculate the elements of the LEFt clinical prediction rule [8]. The rule combines 3 variables: DVT symptoms in the left leg (L); calf circumference of ≥2 cm in the symptomatic leg (E for edema), and presentation in the first trimester (Ft). The patient's LEFt score was not used for clinical decision-making in this study.

2.4 | Outcomes

The primary outcome measure was the rate of objectively diagnosed DVT, pulmonary embolism, or death attributable to VTE in the 3-month follow-up period. Secondary measures included rates of DVT

FIGURE Consort diagram.



and the positive and negative predictive values of scores of 0 to 3 on the LEFt clinical prediction rule, using a positive initial whole-leg CUS or objectively confirmed VTE event during 3-month follow-up as the outcome measure.

2.5 | Follow-up

Patients in whom no DVT was identified on initial whole-leg CUS were followed for 3 months after enrollment for the clinical outcome. We used a method of combined telephone and electronic record review that has been previously reported [6]. Two independent experts with substantial experience in thrombosis research, blinded to original ultrasound result and LEFt criteria, adjudicated all diagnostic studies obtained during the follow-up period. Adjudication also included the reason for institution of any anticoagulant medication, and the cause of any deaths. Telephone interviews were conducted for all patients using a standardized protocol to identify symptoms of VTE, treatment with anticoagulants, diagnostic testing for VTE, diagnosis of VTE, hospitalization, surgery, and general health. We also comprehensively reviewed each patient's electronic medical record, which included all inpatient, outpatient, diagnostic, and pharmacy services. For any deaths, we would obtain and review the clinical records, laboratory, imaging, and death certificate to assess the cause of mortality. Deaths would also be adjudicated by the same 2 reviewers.

2.6 | Statistical analysis

We calculated descriptive statistics for age, symptoms at presentation (pain, tenderness, duration of symptoms), and clinical conditions (number of weeks gestation, recent surgery, recent hospitalization, cancer, congestive heart failure, recent immobilization, cellulitis, superficial vein thrombosis, and family history of thromboembolic disease).

The event rate during 3 months of follow-up of objectively diagnosed VTE and death from thromboembolic disease was calculated for participants with negative initial whole-leg CUS.

The study was planned to enroll 268 patients who meet eligibility criteria so that an exact 95% CI would exclude an event rate of VTE in the observation cohort of 3%. Excluding an event rate of 3% is the commonly accepted standard by which diagnostic strategies are deemed clinically acceptable.

As a secondary analysis, we calculated the LEFt score prospectively for each participant enrolled. We estimated the association between the items of the LEFt clinical prediction rule and the risk of DVT with a chi-squared test or a Fisher test, where applicable. We estimated the proportion of women in each clinical probability group, and the corresponding proportions of confirmed DVT based on initial or follow-up whole-leg CUS results, along with their 95% CIs. No predefined power analysis was performed for this element of the study, as the LEFt score was not used for clinical decision making. All analyses were conducted using R version 4.2.2

TABLE 1 Characteristics of enrolled patients (n = 190).

Characteristic	Participants (N = 190)
Age (y), mean (range)	30 (18-46)
BMI, mean (range)	29.5 (18.7-59.1)
Race and ethnicity, n (%)	
White (non-Hispanic)	163 (85.8)
Hispanic	13 (6.8)
Other	13 (6.8)
Trimester, n (%)	20 (69)
First	19 (10)
Second	67 (35.2)
Third	104 (54.7)
Week of pregnancy, average (range)	28th (4th to 40th)
Gestation type, n (%)	
Singleton	176 (92.6)
Twin	14 (7.4)
Prior pregnancies, average (range)	2 (0 to 13)
Suspected leg, n (%)	
Left	87 (45.8)
Right	79 (41.6)
Bilateral	22 (11.6)

3 | RESULTS

3.1 | Patients

One hundred ninety-four patients met initial inclusion criteria and consented to enroll. Among these, 4 (2.1%) were subsequently excluded; 3 after review revealed the presence of an exclusion criterion (2 patients were found to have prior DVT on review of records, one was already receiving therapeutic anticoagulation at the time of presentation) and one whose informed consent document could not be located. No patient approached for enrollment declined consent (Figure). Enrollment was suspended in April 2019 after enrolling 190 of the planned 268 (70.8%) participants due to the loss of the primary study coordinator. The subsequent emergence of the COVID-19 pandemic precluded study resumption.

Participant characteristics are reported in Table 1. Mean age was 30 (SD 4.9) and mean BMI 29.5 (SD 6.5). There were 19 (10.0%) participants in the first trimester of pregnancy, 66 (34.9%) in the second, and 104 (55.0%) in the third trimester. The average participant was experiencing the third pregnancy (range 1st to 13th).

3.2 | Objective testing for DVT

Whole-leg CUS results were negative on enrollment for 186 (97.9%) participants, for whom anticoagulation was withheld regardless of symptoms or clinical signs. Acute DVT was diagnosed on initial whole-leg CUS in 4 patients (2.1%) (Table 2). All patients with DVT diagnosed on initial whole-leg CUS were treated with therapeutic anticoagulation by their referring clinician.

3.3 | Follow-up

All 186 patients in the cohort with negative initial whole-leg CUS findings completed the minimum follow-up; none were lost to follow-up. No patient received therapeutic anticoagulation for another reason, so all patients were analyzed for the primary outcome.

During 3 months of follow-up, 17 (9.2%) were suspected of DVT and underwent repeat whole-leg CUS. Repeat whole-leg CUS revealed 2 DVTs, for an overall rate of 1.1% (95% CI, 0.2-3.4%) in the 90 days following initial negative ultrasound findings (Table 2). Both patients were diagnosed with femoral DVT of the left leg; one on day 6 following the initial negative CUS findings and the other on day 9. Two patients (1.1%) were suspected of acute pulmonary embolism; neither had pulmonary embolism on computed tomography pulmonary angiogram. There were no deaths.

3.4 | LEFt analysis

One patient did not have leg measurements entered, leaving 189 patients for whom a LEFt score could be calculated (Table 3). In 86 (45.5%) participants, none of the LEFt criteria were present, and one DVT occurred in this group during initial ultrasound (1 of 86; 1.2% [95% CI, 0.05%-5.4%]). In 83 (43.9%) participants, one of the LEFt criteria were present, and 2 DVTs occurred in this group during initial ultrasound (2 of 83; 2.4% [95% CI, 0.38%-7.4%]). In 17 (9.0%) participants, 2 of the LEFt criteria were present; one DVT occurred in this group during initial ultrasound and both DVT events during follow-up were in this group (3 of 17; 17.6% [95% CI, 4.9%-39.0%]). Only 3 participants met all 3 LEFt criteria, and none had DVT. The patient who did not have a LEFt score determined also did not have a DVT event. In the 103 women with at least 1 LEFt criterion, the proportion diagnosed with DVT was not significantly higher (4.9% vs 1.1%, P for difference = .22. Area under the curve (AUC) was 0.649. The resulting sensitivity of a negative LEFt rule was 83.3% (95% CI, 47.3%-98.7%); specificity was 46.4% (95% CI, 39.3%-53.7%); negative predictive value was 98.8% (95% CI, 94.6%-99.9%); positive predictive value was 4.9% (95% CI, 1.8%-10.2%).

4 | DISCUSSION

Despite interrupted recruitment due to the COVID-19 pandemic, this study resulted in 2 key findings. First, in this prospective cohort study of pregnant patients presenting with signs of DVT, the 90-day risk of symptomatic VTE was low when anticoagulation was withheld after a single, negative whole-leg CUS. The rate of VTE during 3 months of

TABLE 2 Characteristics of patients with venous thromboembolism diagnosed at enrollment and follow-up.

	Age, y	Body mass index	Race and ethnicity	Trimester	Week of pregnancy	Gestation type	Prior pregnancies	Site of DVT	Day post -enrollment (days)
DVT diagnosed at enrollment									
Patient 1	29	29	White (non-Hispanic)	First	11th	Singleton	1	Right	0
Patient 1	26	29.1	White (non-Hispanic)	Second	24th	Singleton	2	Left	0
Patient 3	29	21.1	White (non-Hispanic)	Third	32nd	Singleton	2	Right	0
Patient 4	35	31.7	Hispanic	Second	16th	Singleton	0	Left	0
DVT diagnosed during follow-up									
Patient 1	28	27.2	White (non-Hispanic)	Third	34th	Singleton	0	Left femoral	6
Patient 2	22	32.7	White (non-Hispanic)	Second	28th	Singleton	2	Left femoral	9

DVT, deep vein thrombosis.

follow-up was 1.1% (95% CI, 0.05%-3.4%). While the study did not attain full power due to premature closure, the observed rate of VTE suggests that the use of a single, negative whole-leg US to exclude DVT in pregnant patients may be safe, even in the context of low baseline prevalence of disease [13]. Second, these results provide additional evidence that the LEFt clinical prediction rule discriminates between women at low and high risk of DVT, with an AUC of 0.649%.

Our study adds to recent literature examining the performance of diagnostic imaging modalities for DVT in pregnant women. Ultrasound imaging is the preferred modality, given that it poses little if any risk to either the mother or the fetus and is low-cost and widely available. However, DVT is much more likely to be iliofemoral in pregnancy than in nonpregnant individuals, and ultrasound is considerably less sensitive for diagnosing iliofemoral DVT due to the anatomical location and interference from the gravid uterus [14]. Because of these limitations, the *American Society of Hematology* guidelines for diagnosis of VTE in pregnancy recommend imaging iliac veins and serial imaging if the initial ultrasound examination is negative or equivocal [4,5]. A 2006 retrospective cohort study from multiple centers in France identified 0 (0%) VTEs during 3 months of follow-up in 65 pregnant women with a single negative whole-leg ultrasound [15]. Two prospective, multicenter cohorts from France found similarly low 90-day rates of VTE after initial negative whole-leg CUS results, occurring in 2/153 (1.3%) and 0/87 (0%) subjects [10,16]. Our findings are in line with these previous results, and relative strengths of our study include: low loss to follow-up; our reliance on objective, and validated methods of VTE diagnosis during follow-up as our outcome; an independent adjudication committee blinded to patient information, including the LEFt criteria, original ultrasound result and treatment status of the participants, reviewed all follow-up outcomes; enrollment of only

TABLE 3 Analysis of patients according to the items of the LEFt rule and corresponding proportions of confirmed deep vein thrombosis.

Scored population (*n* = 189)				
	Left leg suspected (*n*, %)	**≥2 cm size difference (*n*, %)**	**First trimester (*n*, %)**	**LEFt score (*n*, %)**
	87 (46)	20 (10.6)	19 (10.1)	0: 86 (45.5)
				1: 83 (43.9)
				2: 17 (9.0)
				3: 3 (1.6)
Patients with deep vein thrombosis (at enrollment or follow-up; *n* = 6)				
	Left leg suspected	**≥2 cm size difference**	**First trimester**	**LEFt Score**
Patient 1	No	No	Yes	1
Patient 1	Yes	No	No	1
Patient 3	No	No	No	0
Patient 4	Yes	No	Yes	1
Patient 5	Yes	Yes	No	2
Patient 6	Yes	Yes	No	2

consecutive patients (during coordinator hours) to reduce selection bias; and contact with all participants at 3 months to minimize verification bias. Our findings offer further, high-quality evidence that a single, negative whole-leg CUS is associated with a low risk of subsequent DVT diagnosis in pregnancy. Importantly, given the low prevalence of DVT in our study (common among studies of suspected DVT in pregnancy) and premature study closure that led to imprecision of our estimates, larger, prospective studies and studies combining whole-leg CUS with D-dimer or clinical prediction rules are essential to confirm its safety.

Established clinical prediction tools for DVT in the general population have limited use in pregnant women. The widely used Wells criteria were neither developed nor validated in the pregnant population [17]; they include predictive parameters that are significant risk factors in the general population, such as cancer and recent surgery, but are uncommon in pregnancy; and accordingly, they have been shown to be less sensitive in pregnant patients and the general ambulatory population [18,19]. The LEFt clinical prediction rule was derived and internally validated in pregnant participants and subsequently underwent external validation in a prospective cohort of 157 pregnant patients [8,9]. In the external validation cohort, DVT was diagnosed in 13 of 111 (11.7%) women with at least one LEFt criteria, as compared with none of the 46 (0%) women with none of the LEFt criteria, with an AUC of 0.84. Our observations were similar, with an AUC of 0.649% in our study population. An ongoing prospective clinical study is examining whether combining the LEFt rule with D-dimer testing improves diagnostic accuracy of DVT in pregnant women (NCT02507180) [5]. Our results support designing future studies examining the combination of whole-leg CUS and the LEFt clinical prediction rule, such as recommending against whole-leg CUS in those with LEFt score of 0 or serial whole-leg CUS in those with higher LEFt scores in pregnancy.

There are limitations to our study. Enrollment was halted before accruing the prespecified number of participants, which reduces the precision of our rate estimate. We limited enrollment to patients in the antepartum, but the risk for pregnancy-associated DVT persists for several weeks postpartum, and our protocol did not address this important patient group. We did not measure D-dimer, as its use in pregnant patients was not well developed at the time the study was designed. Participants were followed for 3 months. If DVTs occurred beyond this period and were missed, then this would reduce the negative predictive value found in our study. Enrollment of consecutive eligible patients was limited by coordinator working hours and a comprehensive screening log was not maintained due to the small percentage of the overall population undergoing ultrasound that was pregnant. Our study was conducted in a single center with highly trained, certified vascular technologists. While we planned to exclude women in whom there were technical problems performing the ultrasound, no such exclusions occurred. Nevertheless, although our center has extensive experience and training in whole-leg CUS, studies of whole-leg CUS have been reported across more than 200 centers, suggesting that the technique can be widely adopted [20]. We are unable to ascertain referrals to outside our institution for suspected DVT, but given our system includes an integrated payer, it is unlikely a significant portion of patients would be referred to other facilities, nor that such a population would differ in clinical characteristics. Our rate of detected DVT was very low, but this is consistent in studies assessing suspected VT in pregnancy, as clinicians likely maintain a high index of suspicion and prioritize avoiding missed disease [21]. Finally, our study is comprised of predominately White participants. Future studies should strive for representativeness in participants and maximal inclusivity to ensure generalizability of whole-leg CUS in all pregnant people.

5 | CONCLUSIONS

We observed a low rate of VTE when anticoagulation is withheld following a single, negative whole-leg US in pregnant patients with symptoms of DVT. In addition, the LEFt clinical prediction rule can identify pregnant patients at low risk of DVT. These 2 diagnostic strategies should be further tested in larger, prospective studies to determine their role in diagnosis of DVT in the pregnant population.

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AUTHOR CONTRIBUTIONS

V. Aston, T.F. Porter, W. Branch, S.C. Woller, G.L. Snow, and S.M. Stevens contributed to the conception/design of the study and were involved in data acquisition. A.L. Parks, G.L. Snow, and S.M. Stevens were involved in analysis/interpretation of data. All authors were involved in manuscript writing and/or critically reviewing the manuscript and approving the final version for submission.

RELATIONSHIP DISCLOSURE

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REFERENCES

[1] James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol*. 2006;194:1311–5.

[2] Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. *N Engl J Med*. 2008;359:2025–33.

[3] Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. *J Thromb Haemost*. 2010;8:998–1003.

[4] Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2:3317–59.

[5] Kalaitzopoulos DR, Panagopoulos A, Samant S, Ghalib N, Kadillari J, Daniilidis A, et al. Management of venous thromboembolism in pregnancy. *Thromb Res*. 2022;211:106–13.

[6] Stevens SM, Elliott CG, Chan KJ, Egger MJ, Ahmed KM. Withholding anticoagulation after a negative result on duplex ultrasonography for suspected symptomatic deep venous thrombosis. *Ann Intern Med*. 2004;140:985–91.

[7] Johnson SA, Stevens SM, Woller SC, Lake E, Donadini M, Cheng J, et al. Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. *JAMA*. 2010;303:438–45.

[8] Chan WS, Lee A, Spencer FA, Crowther M, Rodger M, Ramsay T, et al. Predicting deep venous thrombosis in pregnancy: out in "LEFt" field? *Ann Intern Med*. 2009;151:85–92.

[9] Righini M, Jobic C, Boehlen F, Broussaud J, Becker F, Jaffrelot M, et al. Predicting deep venous thrombosis in pregnancy: external validation of the LEFT clinical prediction rule. *Haematologica*. 2013;98:545–8.

[10] Le Moigne E, Genty C, Meunier J, Arnoult AC, Righini M, Bressollette L, et al. Validation of the LEFt score, a newly proposed diagnostic tool for deep vein thrombosis in pregnant women. *Thromb Res*. 2014;134:664–7.

[11] Van der Pol LM, Mairuhu ATA, Tromeur C, Couturaud F, Huisman MV, Klok FA. Use of clinical prediction rules and D-dimer tests in the diagnostic management of pregnant patients with suspected acute pulmonary embolism. *Blood Rev*. 2017;31:31–6.

[12] Talbot SR. B-mode evaluation of peripheral veins. *Semin Ultrasound CT MR*. 1988;9:295–319.

[13] Dronkers CEA, van der Hulle T, Le Gal G, Kyrle PA, Huisman MV, Cannegieter SC, et al. Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017;15:1040–3.

[14] Chan WS, Spencer FA, Ginsberg JS. Anatomic distribution of deep vein thrombosis in pregnancy. *CMAJ*. 2010;182:657–60.

[15] Le Gal G, Prins AM, Righini M, Bohec C, Lacut K, Germain P, et al. Diagnostic value of a negative single complete compression ultrasound of the lower limbs to exclude the diagnosis of deep venous thrombosis in pregnant or postpartum women: a retrospective hospital-based study. *Thromb Res*. 2006;118:691–7.

[16] Le Gal G, Kercret G, Ben Yahmed K, Bressollette L, Robert-Ebadi H, Riberdy L, et al. Diagnostic value of single complete compression ultrasonography in pregnant and postpartum women with suspected deep vein thrombosis: prospective study. *BMJ*. 2012;344:e2635.

[17] Wells PS, Hirsh J, Anderson DR, Lensing AA, Foster G, Kearon C, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet*. 1995;345:1326–30.

[18] Cohen SL, Feizullayeva C, McCandlish JA, Sanelli PC, McGinn T, Brenner B, et al. Comparison of international societal guidelines for the diagnosis of suspected pulmonary embolism during pregnancy. *Lancet Haematol*. 2020;7:e247–58.

[19] Hendriksen JMT, Geersing GJ, Lucassen WAM, Erkens PM, Stoffers HE, van Weert HC, et al. Diagnostic prediction models for suspected pulmonary embolism: systematic review and independent external validation in primary care. *BMJ*. 2015;351:h4438.

[20] Stevens SM, Woller SC, Graves KK, Aston V, Jones J, Snow G, et al. Withholding anticoagulation following a single negative whole-leg ultrasound in patients at high pretest probability for deep vein thrombosis. *Clin Appl Thromb Hemost*. 2013;19:79–85.

[21] Stals MAM, Moumneh T, Ainle FN, Aujesky D, van Bemmel T, Bertoletti L, et al. Noninvasive diagnostic work-up for suspected acute pulmonary embolism during pregnancy: a systematic review and meta-analysis of individual patient data. *J Thromb Haemost*. 2023;21:606–15.