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by Marc Righini, Christelle Jobic, Françoise Boehlen, Jean Broussaud, François Becker, Morgan Jaffrelot, Marc Blondon, Bruno Guias, and Grégoire Le Gal

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Predicting deep venous thrombosis in pregnancy: external validation of the "left" clinical prediction rule

Short title: "LEFt" rule for DVT in pregnancy

[1]Marc Righini, [2]Christelle Jobic, [1]Françoise Boehlen, [3]Jean Broussaud, [1]François Becker, [4]Morgan Jaffrelot, [1]Marc Blondon, [5]Bruno Guias, [2]Grégoire Le Gal, and the EDVIGE study group

[1]Division of Angiology and Hemostasis, Department of Medical Specialties, Geneva University Hospital and Faculty of Medicine, Geneva, Switzerland;
[2]Université de Brest, INSERM CIC 05-02; CHU de la Cavale Blanche, Brest, France;
[3]Department of Vascular diseases, Centre hospitalier Bretagne Atlantique, Vannes, France; [4]Emergency Department, CHU de la Cavale Blanche, Brest, France,
and [5]Vascular medicine physician, Morlaix, France

Correspondence

Marc Righini, MD, Division of Angiology and Hemostasis, Department of Medical Specialties, Geneva University Hospital and Faculty of Medicine, 4 rue Gabrielle-Perret-Gentil CH-1211 Geneva 14, Switzerland. Phone: international +41.223729294.
Fax: international +41.223729299. E-mail: marc.righini@hcuge.ch

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ABSTRACT

Background. The assessment of clinical probability represents an important step in the diagnostic strategy of patients with suspected deep vein thrombosis. The recently derived "LEFt" clinical prediction rule for pregnant women combines three variables: symptoms in the left leg ("L"), calf circumference difference ≥ 2 centimeters ("E" for edema) and first trimester presentation ("Ft"), but is lacking an external validation.

Design and Methods. The LEFt rule was computed among pregnant women with suspected deep vein thrombosis who were included in a multicentre prospective diagnostic management outcome study. We calculated the proportion of women and the prevalence of deep vein thrombosis in each probability group, along with the diagnostic performances of the LEFt rule.

Results. All variables needed to compute the rule could be retrieved in 157 out of the 167 pregnant women with suspected deep vein thrombosis. The prevalence of confirmed deep vein thrombosis was 13/157 (8.3%). The "LEFt" rule was negative in 46 (29%) women. A deep vein thrombosis was diagnosed in 13/111 (11.7%, 95% CI: 8.3 to 20.9%) of women with at least one of the "LEFt" criteria, as compared with 0/46 (0.0%, 95% CI: 0.0 to 7.9%) of women with none of the "LEFt" criteria.

Conclusions. These results suggest that a negative "LEFt" rule accurately identifies pregnant women in whom the proportion of confirmed deep vein thrombosis appears to be very low. The rule should not be used as stand-alone test for excluding DVT during pregnancy but might rather be implemented in a diagnostic strategy in association with D-dimer measurement and compression ultrasonography.

The original trial was registered at clinicaltrials.gov (NCT 00740454).

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INTRODUCTION

During pregnancy, an accurate diagnosis is required in case of suspected deep vein thrombosis (DVT). Indeed, false positive tests lead to inappropriate anticoagulant treatment, which increases the risk of bleeding and requires daily heparin injections during the entire pregnancy. Conversely, false negative tests might lead to a life-threatening thromboembolic event.

Clinical probability assessment by a clinical prediction rule (CPR) is a crucial step in the diagnostic management of a suspected DVT. However, the most commonly used CPR for DVT (the Wells' score) (1), has never been validated in pregnant women. This rule is not suited to the setting of pregnancy, since it includes items that are unlikely to be present in this younger and healthier population (e.g. age >65, cancer, recent surgery). Moreover, the diagnostic performance of clinical signs and symptoms is altered during pregnancy because pregnant women often experience symptoms compatible with DVT, and DVT symptoms may be different during pregnancy (2). On the other hand, some clinical findings, such as the left side presentation, may be more helpful during pregnancy. Finally, the proportion of confirmed DVT is lower in this setting than in other populations, (3, 4), which may influence the performance of CPR (5).

Recently, the 'LEFt' clinical prediction rule was derived and internally validated by Chan et al. among 194 pregnant women investigated for a suspected DVT (6). This rule combines three variables: symptoms in the left leg ("L"), calf circumference difference equal or greater than 2 centimeters ("E" for edema) and a first trimester presentation ("Ft"). They found no DVT among the 89 (46%) of women with none of the "LEFt" criteria, but 7 out of the 105 (16.2%) women with at least one "LEFt" criterion.

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However, before the use of this clinical prediction rule may be recommended in clinical practice, external validation in an independent cohort is required. Thus, our aim was to externally validate the “LEFt” rule among pregnant women included in a prospective diagnostic management outcome study in Europe.

DESIGN AND METHODS

Study design

The study was extensively reported elsewhere (7). Briefly, all consecutive pregnant or post-partum women referred for a suspicion of DVT to two tertiary care centers and 18 vascular medicine private practices between January 2006 and June 2009 were included in this study. Exclusion criteria included an age less than 18 years, a suspicion of an associated PE, an ongoing anticoagulant treatment, an inability to give informed consent and an impossible follow-up. The study was approved by the ethics committee at each institution.

Standardized report forms were filled in for all patients, recording general characteristics, risk factors and clinical signs of VTE.

All included women underwent a complete lower limb high-definition B-mode compression ultrasonography (CUS). DVT was ruled out in patients with a negative compression test and no visualized thrombus. DVT was diagnosed in case of lack of compressibility of a deep vein and, for the iliac vein, in case of absence of Doppler flow or direct visualization of a thrombus.

All women with negative results of complete CUS were left without anticoagulant treatment and were followed-up for a three-month period. At the end of follow-up, all

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women were seen in clinic or interviewed by phone by the study personnel using a standardized questionnaire to gather information about the three-month period following the CUS. All suspected events were adjudicated by an independent adjudication committee that was blinded to the LEFt score.

Study analysis

Of the 210 women included in our diagnostic management study, the 43 postpartum women were excluded, leaving 167 available for this analysis.

The LEFt score was computed post hoc, on prospectively collected data. We estimated the association between the items of the CPR and the risk of DVT with a Chi-Square test or a Fischer test, where applicable. We computed the “LEFt” score, and estimated the proportion of women in each clinical probability group, and the corresponding proportions of confirmed DVT, along with their 95 percent confidence intervals (95% CIs). All analyses were performed using SPSS 19.0 (IBM Inc, Somers, NY, USA).

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RESULTS

Between January 2006 and July 2009, we consecutively included 167 pregnant women with suspected DVT. Data to compute the LEFt rule was missing for 10 women (6%), leaving 157 women available for this analysis. General characteristics of these 157 women are shown in Table 1. Mean age was 32 years (SD 6 years). There were 20 women included during the first, 46 included during the second, and 91 included during the third trimester of pregnancy. Overall, DVT was confirmed in 13 (8.3%) women during the initial evaluation, all of them involving proximal deep veins.

Table 2 displays the repartition of women according to items from the “LEFt” clinical prediction rule, along with the corresponding proportions of confirmed DVT. A suspicion in the left leg and the presence of edema were both significantly associated with the risk of DVT (OR 5.5, 95%CI 1.2-25.7; OR 8.2, 95%CI 2.4-28.4), while the association with the presentation during the first trimester, the third item of the LEFt rule, approached statistical significance (OR 3.6, 95%CI 1.0-12.9) (Table 2).

The proportion of confirmed DVT increased with increasing LEFt rule scores (Table 3). Fourty-six women (29.3%) and 111 women (70.7%) were classified with an unlikely (no criteria) and likely (at least 1 criteria) probability of DVT, respectively (Table 3).

The repartition of women according to the number of criteria of the “LEFt” rule is shown in Table 3. The receiving operator characteristics (ROC) curve is displayed in Figure 1. Area under the curve was 0.84 (95% CI: 0.73 to 0.94). In 46 women (29.3%), none of the criteria were present. No women in this group had a DVT either during the initial investigation or follow-up: 0/46, 0.0% (95% CI: 0.0 to 7.7%). The proportion of DVT was significantly higher in women with at least one criterion: 13/111, 11.7% (95% CI: 8.3 to 20.9). A negative “LEFt” rule had the following accuracy indices: sensitivity 100% (95%

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CI: 77 to 100%), specificity 32% (95% CI: 25 to 40%), negative predictive value 100% (95% CI: 92 to 100%), positive predictive value 12% (95% CI 7 to 19%), negative likelihood ratio 0.0 (-) (Table 3).

DISCUSSION

In this study we found that the “LEFt” rule accurately discriminates pregnant women with suspected DVT. Indeed, the proportion of DVT in patients with zero, one, two and three points was of 0/46 (0.0%), 4/83 (4.8%), 7/24 (29.2%) and 2/4 (50%), respectively. Area under the ROC curves was 0.84 (95%CI: 0.73-0.94).

To our knowledge this is the first external validation of the “LEFt” rule. We found similar diagnostic performances to what was reported in the original paper: 100% sensitivity and negative predictive value. However the proportion of patients with none of the “LEFt” criteria was somewhat lower in our study: 29% as compared with 46% in the study by Chan et al. (6).

To date, no formal clinical probability assessment tool was available for suspected DVT during pregnancy. When assessing clinical probability, using a reproducible and accurate CPR is highly desirable. Indeed, empirical assessment of clinical probability may be associated with some limitations in pregnant women: infrequent situation, modified signs and symptoms, fear from venous thromboembolism (VTE) complications. In particular, the empirical clinical probability assessment is nor standardizable neither easily transmitted to less experienced clinicians. Moreover, the often-used Wells rule has not been derived or validated in pregnant women.

As compared with previously reported clinical prediction rules in VTE, the “LEFt” rule appears to perform impressively well. Indeed, 1) the area under the ROC curve for the

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revised Geneva score for suspected PE and the Wells score for PE and DVT (8, 9) are usually around 0.7; 2) no clinical prediction rule to date has been able to identify a subgroup of patients with a null risk of confirmed VTE (5). Admittedly, the altered clinical presentation and lower threshold for suspicion in pregnant women accounts for the lower prevalence of DVT, which in turn improves the diagnostic performances of the rule (5). Pooling our results with those of Chan et al, 0 out of 135 patients with a negative “LEFt” rule had DVT, corresponding to an upper limit of the 95 percent confidence interval of 2.8%. Of course, the rule should not be used as stand-alone test for excluding DVT during pregnancy. Further prospective studies need to be performed to validate this result.

How should the rule be used in everyday clinical practice? As previously stated the rule should not be used as an exclusion tool. Indeed, even if none of the 46 women presenting without any of the LEFt criteria had a DVT during the 3-month formal follow-up [0/46, 0.0% (95% CI: 0.0 to 7.7%)], the upper limit of the 95% CI remains quite high and does not allow to safely rule out DVT in this particular population. This is obviously in relation with the limited sample of the study. Identifying a subgroup at very low risk could be useful to simplify the diagnostic work-up. For example, D-dimer levels increase during pregnancy and their usefulness is therefore reduced in this setting (9). The “LEFt” rule might be useful in combination with moderately sensitive D-dimer assays (3) or using highly sensitive D-dimer tests with adapted threshold (10, 11). Conversely, women with high “LEFt” score might require more extensive work-up, such as serial CUS, other imaging modalities, or close clinical follow-up. As a matter of fact, the two women in our study who experienced a thromboembolic event during the three months following a negative CUS had two points in the “LEFt” rule at initial presentation.

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Of note, three more steps are missing before its implementation in daily clinical practice may be recommended. First, its diagnostic performance should be prospectively verified in an independent cohort of pregnant women. Second, its usefulness in a standardized diagnostic strategy should be assessed. For example, whether a higher threshold (e.g. low risk if less than 2 LEFt criteria) could be used to increase the usefulness of the rule without altering its safety, needs to be determined. Third, an impact study analysis should demonstrate that the use of the rule changes clinicians behaviour, improves outcomes and reduces costs (12).

Some other findings deserve comments. First, we confirm the very large predominance of left leg involvement in pregnancy related DVT: 11/13 (85%) of DVTs were left-sided. Also, all the diagnosed DVTs were proximal in our study whereas out of the context of pregnancy half of DVTs are limited to the calf (13).

Our study has some limitations. First, the reference standard for DVT in our study was based on a single complete CUS (7). Although the three-month thromboembolic risk in pregnant patients with a negative complete CUS was shown to be low enough to safely rule out DVT in a previous retrospective study (14), this result has not been reproduced by other investigators yet. Second, this is a *post-hoc* analysis. The rule was computed *a posteriori* after completion of the study. Third, our sample size was relatively limited, which turned in wide confidence intervals around estimated proportions and diagnostic accuracy indices.

In conclusion, our study suggests that the “LEFt” rule is accurate in identifying pregnant patients at very low risk of DVT. Further studies need to be performed to clarify its role in the diagnostic management of pregnant women with suspected DVT.

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AUTHORSHIP AND DISCLOSURES

This manuscript represents original work, and it is not under consideration for publication elsewhere. It has never been neither submitted nor published in another scientific journal. All authors meet criteria for authorship and none of the authors have any conflict of interest. All had access to all data in the study, read, approved the final manuscript, and held responsibility for the decision to submit it for publication. The original trial was registered at clinicaltrials.gov (NCT 00740454).

MR-concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, final approval of the manuscript

CG-acquisition of data, analysis and interpretation of data, critical revision of the manuscript, final approval of the manuscript

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GLG- concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, final approval of the manuscript

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Contributors from the EDVIGE study group

Mohamed BABA-AHMED (Algiers), Dominique BERNARD (Carhaix), Henri BOUNAMEAUX (Genève), Luc BRESSOLLETTE (Brest), Paul CIRAFICI (Geneva), Cécile DE GAIL SAUTERON (Saint-Grégoire) , Philippe DE MOERLOOSE (Genève), Aurélien DELLUC (Brest), Marie-Annick DIRER (Brest), Catherine DUIGOU-BIHi

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(Lorient), Pierre FONTANA (Geneva), Jacques GESTIN (Quimper), Salah GUEDDI (Geneva), Bruno GUICHAOUA (Quimper), Patrice HUDO (Saint-Brieuc), Nathalie JOURNEAUX (Rennes), Raymond KACZMAREK (Quimper), Geneviève KERCRET (Rennes), Marie-Luce LABALETTE (Lannion), Dominique LE BERRE (Paimpol), Isabelle LEBORGNE (Rennes), Marie-Pierre LE GOC PEDELUCQ (Lorient), Dominique LE MENN BUREAU (Pontivy), Fabrice LE THOER (Brest), Patrick LOUIS (Brest), Stéphanie LOUIS (Brest), Geneviève MADEC BOUGEARD (Lannion), Mario MAUFUS (Grenoble), Catherine NOEL MOREL (Pacé), Karine PICHON (Vannes), Emmanuel PLAT (Brest), Laurent PRUVOST (Saint-Malo), Philippe QUEHE (Brest), Edith RIVOAL (Quimper), Eric THULLIEZ (Rennes), Johny VOGEL (Sierre), Robert WUTSCHERT (Neuchatel).

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TABLES AND FIGURES

Table 1. General characteristics of included patients.

Characteristics	
Age, m (SD), years	32.0 (6)
BMI, m (SD), kg/m^2	25.3 (5.2)
Weight gain, m (SD), kg	+9.1 (5.4)
Stage of pregnancy, n (%)	
First trimester	20 (12.7)
Second trimester	46 (29.3)
Third trimester	91 (58.0)
Risk factors	
Personal history of VTE, n (%)	19 (12.3)
Family history of VTE, n (%)	31 (20.8)
Known thrombophilia, n (%)	7 (4.8)
Recent immobilization, n (%)	12 (8.0)
Recent surgery or trauma, n (%)	0 (0.0)
Varicose veins, n (%)	48 (31.8)
Complicated pregnancy*, n (%)	11 (7.3)
Twin pregnancy, n (%)	5 (3.4)
Recent travel (> 6 hours), n (%)	11 (7.3)

* Complicated pregnancy encompassed gestational diabetes, pre-term labor, intra-uterine growth restriction, pre-eclampsia, placenta praevia, ovarian hyperstimulation syndrome.

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Table 2. Repartition of patients according to the items of the “LEFt” rule and corresponding proportions of confirmed DVTs.

	N,(%)	DVT N, (%)	Odds ratio, (95%CI)	p
Side of suspicion				
Left	83 (52.9)	11 (13.3)	5.5 (1.2-25.7)*	0.017
Right	67 (42.7)	2 (3.0)		
Bilateral	7 (4.5)	0 (0.0)		
Edema (calf circumference difference ≥ 2 cm)				
Yes	40 (25.5)	9 (22.5)	8.2 (2.4-28.4)	<0.001
No	117 (74.5)	4 (3.4)		
Pregnancy trimester stage				
First	20 (12.7)	4 (20)	3.6 (1.0-12.9)*	0.07
Second	46 (29.3)	0 (0.0)		
Third	91 (58.0)	9 (9.9)		

* The odds ratio corresponds to the comparison of the first with the two remaining categories

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Table 3. Diagnostic performances of the “LEFt” rule.

	n,(%)	Proportion of DVT n, (%)	p
LEFt score (points)			
0	46 (29.3)	0 (0.0)	< 0.001
1	83 (52.9)	4 (4.8)	
2	24 (15.3)	7 (29.2)	
3	4 (2.5)	2 (50.0)	
LEFt score			
0 (unlikely)	46 (29.3)	0 (0.0)	0.002
≥1 (likely)	111 (70.7)	13 (11.7)	

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Legend for figure

Figure 1: The “LEFt” score for DVT in pregnant women: ROC curve analysis

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Figure 1. LEFT rule for the diagnosis of DVT in pregnancy: receiver operating characteristics (ROC).