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ORIGINAL ARTICLE

Personalized thromboprophylaxis using a risk score for the management of pregnancies with high risk of thrombosis: a prospective clinical study

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Essentials

- Pregnancy is a risk factor for thrombosis.
- Management of thrombosis risk in pregnancy remains a challenge.
- Prophylaxis needs to be personalized.
- Our score may be a helpful tool for the management of pregnancies at high risk of thrombosis.

Summary. *Background:* Patients with thrombophilia and/or a history of venous thromboembolism (VTE) are at risk of thrombosis during pregnancy. A risk score for pregnancies with an increased risk of VTE was previously described by our group (Lyon VTE score). *Objectives:* The aim of this prospective study was to assess the efficacy and safety of our score-based prophylaxis strategy in 542 pregnancies managed between 2005 and 2015 in Lyon University Hospitals. *Patients/Methods:* Of 445 patients included in the study, 36 had several pregnancies during the study period. Among these 445 patients, 279 had a personal history of VTE (62.7%), 299 patients (67.2%) had a thrombophilia marker, and 131 (29.4%) thrombophilic women had a personal history of VTE. During pregnancy, patients were assigned to one of three prophylaxis strategies according to the risk scoring system. *Results:* In the antepartum period, low molecular weight heparin (LMWH) prophylaxis was prescribed to 64.5% of patients at high risk of VTE. Among them, 34.4% were treated in the third trimester only, and 30.1% were treated throughout pregnancy. During the postpartum period, all patients received LMWH for at least 6 weeks. Two antepartum-related VTEs (0.37%; one with a score of < 3 and the other with a score of > 6) and four postpartum-related VTEs (0.73%; three with scores of 3–5 and one with a score of > 6) occurred. No case of pulmonary embolism was observed during the study period. The rate of bleeding was 0.37%. No serious bleeding requiring transfusions or surgery occurred during the study period. *Conclusion:* The use of a risk score may provide a rational decision process to implement safe and effective antepartum thromboprophylaxis in pregnant women at high risk of VTE.

Keywords: low molecular weight heparin; Lyon VTE score; pregnancy; prophylaxis; venous thromboembolism.

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Introduction

Venous thromboembolism (VTE) can occur at several key periods in a woman's lifetime: for example, the risk of VTE is four to five times higher in pregnant women than in non-pregnant women of the same age [1–3]. This risk is 10 times higher during the postpartum period [4–6]. The risk of VTE exists throughout pregnancy, but the risk may increase as the pregnancy progresses [7], and the risk of fatal pulmonary embolism (PE) is higher during the third trimester and postpartum [4,5,7].

The main risk factors for developing VTE during pregnancy include a personal history of VTE, a patient age of > 35 years, and hereditary or acquired thrombophilia.

An individual assessment of the VTE risk is crucial for optimal thromboprophylaxis, but there is no validated tool to help clinicians stratify the risk in pregnant women and introduce prophylactic anticoagulation at the appropriate time. Recommendations mostly based on case–control studies and expert opinions do not accurately reflect the physician's need, and the management of VTE risk in pregnancy remains a challenge. The use of a risk stratification tool that takes all individual risk factors for VTE into consideration and that aids in making decisions regarding prophylaxis regimens may help. Our group has previously described a VTE risk score (the Lyon VTE score), rating patients at increased risk of VTE and recommending individually tailored management [8]. A retrospective evaluation of the initial score showed favorable outcomes in pregnancies with a high risk of thrombosis [8]. A subsequent multicenter prospective study reported promising results with a modified version of this score and a related management strategy [9]. We wanted to evaluate this score prospectively in a larger population while excluding patients receiving long-term anticoagulants, those with antithrombin deficiency, and those with antiphospholipid syndrome, for whom clear recommendations exist [10–12]. Thus, the main objective of this study was to evaluate the efficacy and tolerability after 10 years of prospective use of the Lyon VTE score in daily practice to guide the prescription of antithrombotic prophylaxis during pregnancy.

Materials and methods

Patients

There were 566 eligible, consecutive pregnant patients at high risk of VTE, referred to the Clinical Hemostasis Unit of Lyon University Hospitals, during the study period between 1 January 2005 and 1 January 2015.

Inclusion criteria

Pregnant patients included in the study were those at risk of thromboembolism because of a history of VTE and/or a confirmed inherited thrombophilia marker: protein C or S deficiency, factor V Leiden mutation, or prothrombin G20210A mutation.

Exclusion criteria

The exclusion criteria were: contraindication to heparin therapy, obstetric complications only, with no history of VTE (pre-eclampsia, HELLP [hemolysis, elevated liver enzymes, low platelet count], intrauterine growth retardation, miscarriage, etc.), a history of superficial venous thrombosis, and those having the highest VTE risk, for whom clear recommendations with a high level of evidence are available (patients receiving long-term anticoagulants, or those with antiphospholipid syndrome or antithrombin deficiency).

The Lyon VTE score

The Lyon score was first described in 2005 [8]. This score was established according to data from the literature, and tested retrospectively and blindly. This encouraged the performance of a prospective study of a larger number of patients, and the modified score was validated in a second prospective multicenter study [9].

The score assessed VTE risk during pregnancy according to three main criteria: (i) history of VTE; (ii) known thrombophilia markers; and (iii) contemporary risk factors dependent on the current pregnancy. In each category, only one point was assigned to the item presenting the lowest risk factor, and the score was balanced for other items in accordance with the estimated risk degree available in the literature (Table 1).

Table 1 Score for the assessment of the risk of pregnancy-related venous thromboembolism (VTE)

Risk factor	Venous thromboembolism	Score
Personal history of VTE	History of VTE related to pregnancy (occurred during the antepartum period), or cerebral vein thrombosis or massive PE or VTE in childhood (age < 16 years)	6
	Spontaneous or estrogen-induced PE or proximal DVT	3
	Transient risk factor-induced PE or proximal DVT	2
	Spontaneous or estrogen-induced distal calf DVT	2
	Transient risk factor-induced distal calf DVT	1
If there is a personal history of VTE	Recurrent VTE history	3
	Residual venous thrombi with clinical signs of post-thrombotic syndrome	3
	Recent VTE history < 2 years	2
Thrombophilia	Homozygous mutations, combined thrombophilia risk factors	3
	Protein C deficiency, protein S deficiency, heterozygous *F5* G1691A mutation, heterozygous *F2* G20210A mutation	1
	If no hypercoagulability detected, family history of severe or recurrent VTE	1
Other risk factors	Bed rest, immobilization	2
	Twin pregnancy	1
	Age > 35 years	1
	Body mass index of > 30 kg m^{-2}	1

DVT, deep vein thrombosis; PE, pulmonary embolism. Total score = No. antenatal prophylaxis if the score is < 3. Early heparin prophylaxis in patients with a score of ≥ 6. Low molecular weight heparin was prescribed only in the third trimester to patients with a score between 3 and 5.

Regarding the risk factors associated with a history of VTE, we took into account the circumstances of the occurrence of thrombotic events (spontaneous or with transitory risk factors), location and severity of the venous thrombosis, and age of onset of the first episode. We attributed the least important risk factor (1 point) to distal deep vein thrombosis (DVT) history with triggering factor and the weighted coefficient based on whether it was spontaneous or not and depending on the severity of the thrombotic history. The major risk factor (6 points) was attributed to a personal history of DVT occurring during pregnancy. Six points were awarded for serious and/or very unusual thrombotic events, i.e. massive PE, spontaneous or estrogen-induced cerebral vein thrombosis (CVT) and VTE that occurred during childhood before the age of 16 years.

With regard to individual risk factors present during the ongoing pregnancy, we took into account age of > 35 years, obesity, twin pregnancy, and immobilization or bed rest during pregnancy (lying in bed for > 18 h per day).

We attributed an intermediate risk (3 points) to combined thrombophilia markers and homozygous mutations, and gave 1 point to all other inherited thrombophilia conditions. If the thrombophilia screening remained non-informative, a point was given if there was a spontaneous or recurrent family history of VTE in first-degree relatives aged < 60 years.

The result of the score classified patients into three groups:

- For a score below 3, the patient does not receive low molecular weight heparin (LMWH) during the antepartum period.
- If the score is between 3 and 5, a prophylactic dose of LMWH is introduced (enoxaparin 40 mg day^{-1} subcutaneously) in the third trimester.
- If the score is ≥ 6, the prophylactic dose of LMWH is prescribed early during pregnancy.

No patient received therapeutic doses of LMWH during the study.

In all cases, LMWH prophylaxis was prescribed during the postpartum period: 6 weeks in the case of vaginal delivery, or 8 weeks in the case of caesarean section.

Elastic compression stockings (16–20 mmHg) were prescribed systematically to all patients throughout pregnancy and during the postpartum period. All patients had been given advice on the potential benefit of physical activity, and received recommendations against a sedentary lifestyle, if not advised otherwise by the obstetrician in some cases.

Patients underwent a monthly consultation for clinical evaluation. The consultation also enabled new risk factors (bed rest, immobilization, etc.) to be identified that would necessitate a change in score, and therefore adjustment of thromboprophylaxis.

A postpartum consultation was organized 3 months after delivery. It allowed the identification of potential intercurrent events.

Occurrence of thrombotic episodes and/or complications

If there was an episode of acute VTE, we recorded the stage of pregnancy during which it occurred, the location of the thrombosis, the circumstances, and the diagnostic method. The occurrence or absence of complications, such as severe bleeding, heparin-induced thrombocytopenia, symptomatic osteoporosis, and intolerance to injections, requiring a change in treatment was also noted.

Laboratory tests: thrombophilia testing

All patients included in the study underwent thrombophilia screening, including blood count, activated partial thromboplastin time, prothrombin time, fibrinogen, antithrombin activity and antigen levels, protein C and protein S activity and antigen levels, lupus anticoagulant, anticardiolipin antibodies and anti-β_2-glycoprotein 1 antibodies, and FV Leiden and prothrombin gene mutations. Tests were performed in the majority of cases before the pregnancy, in the same hemostasis laboratory as described previously [9]. Eleven asymptomatic women with family history of VTE and known thrombophilia in the family (eight FV Leiden and three prothrombin gene mutations) were diagnosed during pregnancy.

Data analysis

A questionnaire was completed for each pregnancy. It included an inclusive record, score calculation, and an evaluation form extending to 3 months after delivery. Information collected at baseline included the identity of the patient, age, weight, height, smoking habit, number of pregnancies, history of vascular-placental pregnancy complications, history of miscarriages, character of pregnancy, i.e. spontaneous or as a result of *in vitro* fertilization, VTE history, the existence of a known thrombophilia, and type and presence/absence of a family history of VTE in first-degree relatives.

After collection of the information, the score was calculated for each pregnancy, and patients were divided into three groups: score of < 3, score of 3–5, and score of ≥ 6.

Each group defined the therapeutic approach to be prescribed in terms of antithrombotic prophylaxis during pregnancy.

The last part of the questionnaire related to the postpartum visit at 3 months after delivery. The information gathered was the date of delivery, the weight and the sex of the newborn, the type of delivery, the type of anesthesia, if any, the introduction of LMWH dosage and the duration of treatment, the occurrence or absence of a

VTE event and context, and finally the occurrence or not of complications.

The data analysis was descriptive, with averages and standard deviations (SDs). In cases of incomplete questionnaires, patients and obstetricians were contacted by phone or by mail.

Results

A total of 566 pregnant women with thromboembolic risk were enrolled in the study after informed consent had been obtained. Of these, 99 patients were excluded: two patients had antithrombin deficiency, 10 patients had antiphospholipid syndrome, five patients were on long-term warfarin, 51 patients had thrombophilia associated with early miscarriages, 29 patients had thrombophilia associated with the HELLP syndrome, preeclampsia, eclampsia, *in utero* fetal death, or *in utero* growth restriction, and two patients were seen during early pregnancy for acute DVT and were referred to us for their management. That left 467 patients who were included in the study, but 22 were lost to follow-up. A total of 445 patients completed the study with a full set of data, and their results were analyzed (Table 2). Thirty-six women had several pregnancies (n = 133) and 409 had one pregnancy during the study period. In total, 542 consecutive pregnancies at high risk of VTE, managed in a same way between 2005 and 2015 in Lyon University Hospitals by use of the Lyon VTE score, were analyzed (Fig. 1).

Patients' characteristics

The average age of the patients (542 pregnancies) was 33 years (± 4.8 years) (mean ± SD); 132 patients (29%) were aged > 35 years. The mean body mass index (BMI) was 24.3 kg m^{-2} (± 5.1 kg m^{-2}). Eight patients were morbidly obese (BMI > 35 kg m^{-2}), and 61 (13.7%) patients were active smokers. Of the patients, 190 were primiparous and 255 were multiparous. Twelve pregnancies were twins and 19 patients were prescribed bed rest at the end of their pregnancy to reduce the risk of preterm delivery.

VTE history

A total of 279 (62.7%) patients had a history of VTE, of whom 85 had a proximal DVT of the lower limbs, 121 had a distal calf DVT, 63 had PE, 10 had CVT, 25 had recurrent VTE, and 41 had residual venous thrombi (≥ 2 mm) associated with clinical signs of post-thrombotic syndrome, i.e. pain, edema, heaviness, hyperpigmentation, etc.

Thrombophilia

A total of 299 (67.2%) patients were carriers of thrombophilia markers: 26 patients had a protein C deficiency, 18 had a protein S deficiency (all detected before the pregnancy, in the absence of hormone therapy and confirmed by genotyping), 152 had a heterozygous FV Leiden mutation, nine had a homozygous FV Leiden mutation, 65 had a heterozygous *F2* 20210A mutation, and four had a homozygous *F2* 20210A mutation. Twenty-five patients had combined thrombophilia markers.

Risk of thrombosis as evaluated with the Lyon VTE score (Table 3)

A total of 158 (35.5%) patients had a computed score below 3 (moderate risk) in early pregnancy. Of these patients, 22.7% had a personal history of VTE and 79.1% had thrombophilia.

A total of 153 (34.4%) patients had a score of 3–5 (high risk). Among these patients, 92% had a history of VTE and 66.7% had thrombophilia.

The remaining 134 (30.1%) patients had a score of ≥ 6 (very high risk). All of these patients (100%) had a history of VTE and 41% had thrombophilia.

Thromboprophylaxis by score (Table 2)

Among the 158 patients who were at moderate risk, 139 received LMWH prophylaxis in the postpartum period only, as dictated by the calculated score. Nineteen patients had a change in score from < 3 to 3–5 because of

Table 2 Risk stratification according to the Lyon VTE score, therapeutic strategy, venous thromboembolic events that occurred, and complications.

Lyon VTE score-based strategy for LMWH prophylaxis	Score < 3: no LMWH in antepartum and LMWH in postpartum	Score 3–5: LMWH in the third trimester and LMWH in postpartum	Score ≥ 6: early LMWH in antepartum and LMWH in postpartum
Number of patients, n = 445	158	153	134
Number of pregnancies, n = 542			
Personal history of VTE, no. (%)	36 (22.7)	141 (92)	134 (100)
Thrombophilia, no. (%)	125 (79.1)	102 (66.7)	55 (41)
Prophylaxis with LMWH by score	139 (= 158 − 19)	172 (= 153 + 19)	134
VTE occurred antepartum	1	0	1
VTE occurred postpartum	0	3	1
Bleeding complications	2	0	0

LMWH, low molecular weight heparin; VTE, venous thromboembolism.

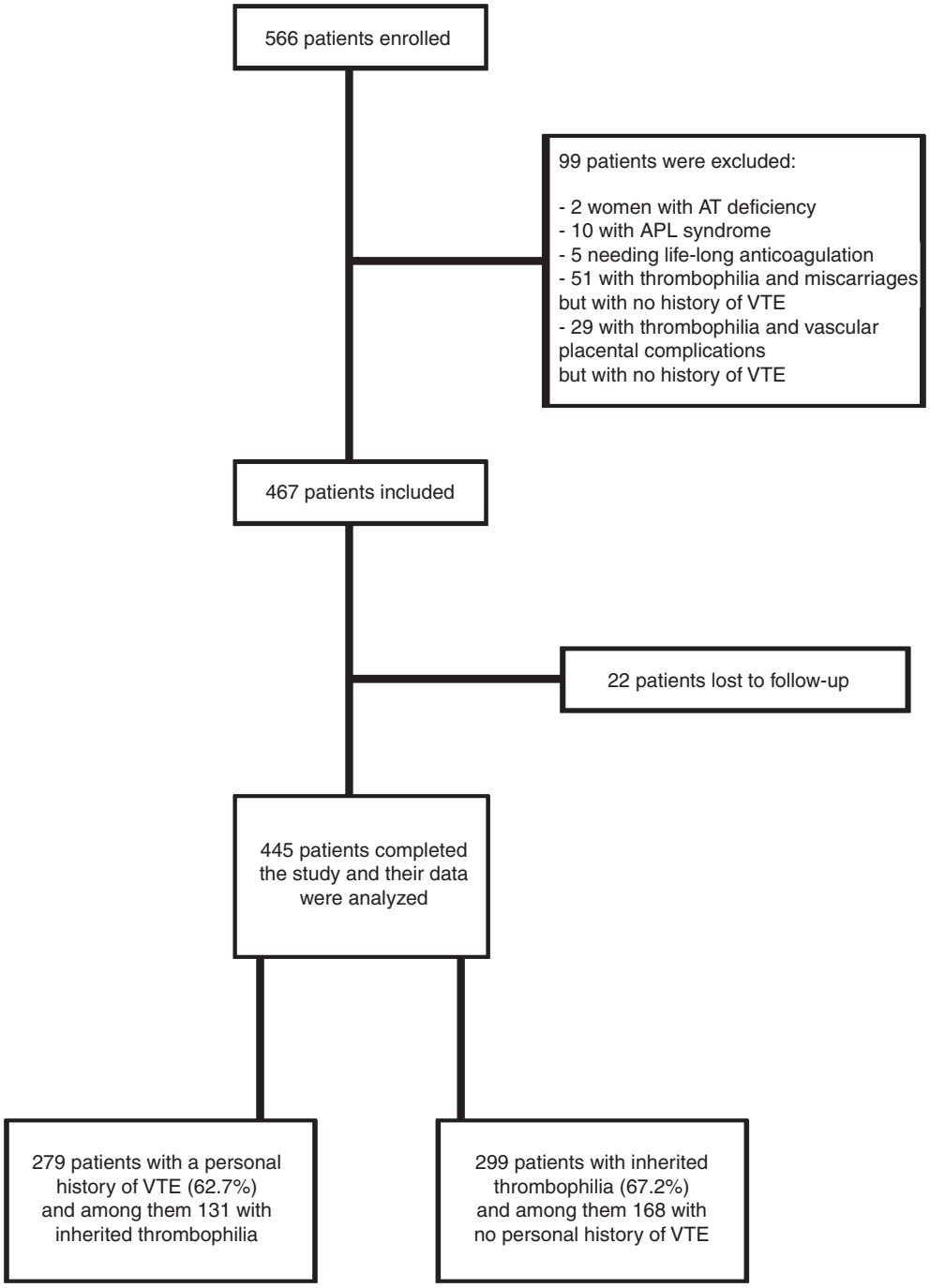

Fig. 1. Patients included in the study. AT, antithrombin; APL, antiphospholipid; VTE, venous thromboembolism.

late pregnancy bed rest to prevent preterm delivery. They therefore received LMWH in the third trimester, joining the middle group. Thus, there were 172 high-risk patients who received prophylaxis in the third trimester and postpartum. The 134 high-risk patients with a score of ≥ 6 were treated during their entire pregnancy.

Eight patients were morbidly obese and therefore received 60 mg daily of enoxaparin instead of 40 mg daily.

Among 542 pregnancies, there were 430 vaginal deliveries and 112 caesarean sections. The mean birth weight of the newborns was 3200 g ($\pm$ 578 g). Patients who underwent vaginal delivery all received LMWH for 6 weeks postpartum, and those delivered by caesarean section received LMWH for 8 weeks postpartum.

Venous thromboembolic events that occurred during the study (Tables 2–4)

During the 10 years of the study, there were six DVT episodes. Of these, two (0.37%) occurred during the

Table 3 Venous thromboembolic events occurring during the antepartum period

Patient characteristics	Score	Prophylactic treatment	VTE events	Time period
Patient no. 1 Age 33 years BMI = 26.3 kg m^{-2} History of spontaneous pulmonary embolism Homozygous *F2* 20210A	6	Enoxaparin 40 mg daily, started at the sixth week of pregnancy	Calf DVT	28th week of pregnancy, despite LMWH prophylaxis
Patient no. 2 Age 29 years BMI = 23.7 kg m^{-2} No history of VTE Heterozygous factor V Leiden	1	No LMWH antepartum	Proximal DVT	Eighth month of pregnancy: after 1 week of bed rest in the absence of LMWH prophylaxis

BMI, body mass index; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

Table 4 Venous thromboembolic events occurring during the postpartum period

Patient characteristics	Score	Prophylactic treatment	VTE events	Time period
Patient no. 1 Age 40 years Morbid obesity, BMI > 37.2 kg m^{-2} History of spontaneous distal DVT Heterozygous factor V Leiden Vaginal delivery	5	Enoxaparin 60 mg daily during the third trimester and for 6 weeks postpartum	Distal DVT	Seventh week postpartum (1 week after LMWH withdrawal)
Patient no. 2 Age 33 years BMI = 22.4 kg m^{-2} History of spontaneous proximal DVT with symptomatic sequelae Heterozygous factor V Leiden Vaginal delivery	7	Enoxaparin 40 mg daily throughout pregnancy and for 6 weeks postpartum	Distal DVT	Seventh week postpartum (1 week after LMWH withdrawal)
Patient no. 3 Age 33 years BMI = 25.1 kg m^{-2} History of spontaneous proximal DVT Protein C deficiency Active smoker Vaginal delivery	4	Enoxaparin 40 mg daily and for 6 weeks postpartum	Pulmonary embolism	12th week postpartum (6 weeks after LMWH withdrawal)
Patient no. 4 Age 31 years BMI = 24.8 kg m^{-2} History of spontaneous pulmonary embolism Heterozygous *F2* 20210A Active smoker Vaginal delivery	5	Enoxaparin 40 mg daily during the third trimester	Ovarian vein thrombosis	3 days after delivery despite postpartum LMWH prophylaxis

BMI, body mass index; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

antepartum period, including one in the lower-score group (< 3) and one in the very high risk group (≥ 6; Table 3).

Four (0.73%) events occurred during the postpartum period, including three in the group with a score of 3–5 and one in the group with a score of ≥ 6 (Table 4).

Thrombotic complications that occurred during pregnancy

Regarding the two events that occurred during the antepartum period, the first patient was aged 33 years, with a history of spontaneous PE and a homozygous *F2* G20210A mutation (score = 6). She received enoxaparin 40 mg daily from the sixth week of pregnancy and wore elastic stockings occasionally, but not every day. She presented with a calf DVT in the 28th week of gestation, despite daily use of anticoagulant therapy.

The second patient was aged 29 years, was heterozygous for the FV Leiden mutation, and did not have a personal history of VTE (score of 1). She presented with a left proximal DVT during a bed rest period in the eighth

month of pregnancy. The obstetrician did not introduce preventive LMWH during this time, despite her having a modified score of > 3.

Thrombotic complications that occurred during the postpartum period

With regard to events that occurred during the postpartum period, three of them took place after anticoagulant withdrawal, in patients who received systematic LMWH during the 6 weeks after delivery. Another patient had an ovarian vein thrombosis despite LMWH prophylaxis. All of these women had several risk factors (age, obesity, thrombophilia, etc.; Table 4).

Bleeding complications

Two (0.37%) patients in the group with a score of < 3 had bleeding: one during delivery, which was not LMWH-related, as the patient had not received LMWH, and one possible LMWH-related mild bleed at the fifth week postpartum while the patient was receiving LMWH prophylaxis. This bleeding required only early cessation of the LMWH. No VTE occurred after cessation of the LMWH.

No case of heparin-induced thrombocytopenia or symptomatic osteoporosis was diagnosed. Four (0.73%) patients were intolerant of subcutaneous enoxaparin injections, and developed urticarial reactions at the injection sites. Symptoms resolved with discontinuation of enoxaparin, and have not returned, despite the introduction of another LMWH.

Discussion

In view of the lack of international recommendations with a high level of evidence regarding prophylactic treatment of pregnant women at risk of thrombosis, many favor personalized care with the use of scores to individually assess the risk and propose appropriate preventive measures.

There are currently five published scoring systems for assessing the antepartum thrombosis risk in pregnant women. It is extremely difficult to compare the performance of these tools, as they are not directed at the same patient population and do not offer the same therapeutic approaches.

Two of these risk scores are directed towards the general obstetric population [13,14], and aim to stratify pregnant women into different risk categories based on the individual characteristics of pregnant women at an obstetric clinic. (i) The Italian pregnancy healthcare program includes 22 risk factors for pregnancy-related VTE. According to this score, patients with a low risk of VTE undergo clinical observation only, those with a moderate risk receive above-knee compression stockings, and those with a high risk receive compression stockings and LMWH. The Italian score was recently evaluated in 1787 pregnant women. Seventy per cent of patients had clinical observation, 25% had compression stockings, and 5% of patients were treated with LMWH and compression stockings. One superficial vein thrombosis was observed during the postpartum period in a patient at low risk [14]. (ii) The Saint-Etienne score results, published in 2008, related to 2690 pregnancies corresponding to a general maternity population. Only 305 women had a VTE score of ≥ 1 and were considered to be at risk of thrombosis. Only 1% of the study population had a personal history of VTE, and 0.7% had thrombophilia. Despite the low number of patients at risk, the authors observed nine thrombotic events. The overall rate of thrombotic events related to pregnancy in this population was 0.33%, and the rate of bleeding was 1.04%. As this score is for the general pregnancy population, this could be compared with the theoretical expected rate of thrombosis during pregnancy, which is estimated to be 1/1000 [15]. The thrombosis rate in this study was approximately three times higher. These data suggest an insufficiently discriminating character of the score with respect to identifying patients at risk. Recently, a new version of the Saint-Etienne score was developed with the Delphi method [16], the results of which are being analyzed.

In contrast to these scores, the German Bauersachs score [17], the UK Schoenbeck score [18] and the Lyon VTE score [8,9] are specifically for pregnant women at risk of thrombosis because of a history of VTE and/or documented thrombophilia. (i) The results of a prospective study evaluating the German score [17], including 810 patients, reported promising results in terms of efficacy, but raised questions about safety, as many patients had serious bleeding (3%). This could partly be explained by the large number of patients treated for at least 9 months, including 116 at curative doses. (ii) The UK score was tested in a small group of 58 pregnant women [18]. No VTE was observed during the study. The authors reported that the use of the scoring system improved the consistency of approach when women at high risk of VTE were advised. The efficacy and safety of this score need to be evaluated in further large-scale prospective clinical studies. (iii) The Lyon VTE score aims only to prevent pregnancy-related VTE for women at high risk of thrombosis. However, it excludes situations associated with very high thrombotic risk for which there are clear international guidelines with a high level of evidence, e.g. antiphospholipid syndrome [19–22] and antithrombin deficiency [19–22]. Unlike the Saint-Etienne score and the German score, the Lyon VTE score does not include miscarriages, fetal deaths, and other vascular-placental disorders. Several studies have reported on the key role of aberrant differentiation of cytotrophoblasts, maternal inflammatory response and oxidative stress in the pathophysiology of vascular-placental disorders [23–25]. Even

though there is a paucity of evidence associated with obstetric complications and thrombophilia [26], the pathophysiology of VTE and that of miscarriages and vascular-placental diseases differ, and these probably require different management strategies.

Our current results confirm previous data [9], showing a thrombosis rate during pregnancy of 0.37%, a postpartum thrombosis rate of 0.73%, and a bleeding rate of 0.37%. Brill-Edwards *et al*. [27] reported a recurrence rate of antepartum VTE of 2.4%, if heparin was withheld, in women with a single episode of venous thrombosis. Tormene *et al*. [28] showed that the frequency of VTE was 6.4% for heterozygous carriers and 16.7% for homozygous carriers of the FV Leiden mutation during pregnancy. Taken together, these results suggest that the score-based management approach developed by our group might be interesting for pregnancies at high risk of VTE.

Among the 445 patients managed by use of the Lyon VTE score, two venous thromboses of the lower extremities occurred during pregnancy. The first was in an asymptomatic patient with a heterozygous FV Leiden mutation who was classified as low risk (score of < 3). The patient had late pregnancy bed rest without prescription of LMWH, and the thrombotic accident occurred after 1 week of bed rest. We note that, in our series, 19 patients had a score change during pregnancy with the early introduction of LMWH treatment, imposed mostly because of bed rest to reduce the risk of premature delivery. These results suggest the importance of clinical monitoring during pregnancy and the need to adapt the strategy to changing risk factors.

The second patient had a distal DVT in late pregnancy when she was already taking prophylactic LMWH; she had been followed since the beginning of pregnancy, as she had a high thrombotic risk (score of > 6). It is be worth noting that the patient preferred not to wear elastic stockings, because of discomfort.

No cases of PE or CVT occurred during the 10 years of the study.

The three scores and international recommendations emphasize the importance of treating all women at risk for at least 6 weeks postpartum [29]. However, despite systematic prevention during this period, thrombotic events still occurred, especially after anticoagulant therapy had been stopped. In our study, four DVTs occurred during the postpartum period. These results suggest that prevention for 6 weeks is probably not enough for the entire population at risk, so individualized care should be considered. The Swedish score [30] is the only one to date that evaluates the postpartum-related risk of VTE and offers customizable postpartum prophylaxis. More recently, Jacobsen *et al*. [31,32] determined the thrombotic risk factors associated with the postpartum period. On the basis of major risk factors reported in the literature, a postpartum score may be developed to personalize the duration of thromboprophylaxis during this time of very high risk.

Femoral vein flow velocity is significantly greater in pregnant women with compression than in those without [33]. All patients included in the study received comprehensive information on the use of elastic stockings, and were encouraged to wear them throughout pregnancy. This may help to reduce venous stasis and, in turn, the number of patients requiring LMWH during pregnancy, as, in our series, only 30% of women at risk received LMWH throughout pregnancy and the incidence of thrombotic complications was not greater than in other published studies. This may also help to reduce the incidence of LMWH-related bleeding complications, which was lower in our study than in the German and Saint-Etienne studies.

The personalized care according to the Lyon VTE score is in line with international recommendations [11,12,22]. However, the major difference between the recommendations and our score-based approach is the possibility of introducing LMWH in the last trimester of pregnancy in women with a moderate risk (score of 3–5). Our patients in this group wear elastic compression stockings from the beginning of the pregnancy, and LMWH is introduced early in the seventh month. Our results show no thrombosis in this group. The thrombotic risk exists throughout pregnancy, with a steady increase in rate during the third trimester and postpartum [4,5,7]. The risk of fatal PE also increases significantly during the third trimester and postpartum [4]. In patients with a moderate risk (score of 3–5), our strategy is to start prophylaxis with elastic stockings and physical activity, and introduce LMWH treatment in late pregnancy. This approach might help to explain the low incidence of bleeding observed in the Lyon series as compared with other scores.

Although there were 445 women at risk of thrombosis in this study, the numbers appear low if we consider the absolute risk of thrombosis. This risk is estimated to be 1/400 in patients with the FV Leiden mutation, the most common thrombophilia. Another major limitation of this study was the lack of specific data on pregnancy regarding the score items. Indeed, in this population, there are no data comparing the risk of thrombotic recurrence according to location and the severity of the first thrombosis. Thus, the score was built according to data from the general population.

Each of the published scores has its limitations, and no score is appropriate for all patients. Nevertheless, this type of tool allows a standardized approach with objective criteria, and can help non-specialized centers and/or young doctors to manage these high-risk pregnancies.

Our data emphasize the need for individualization of antithrombotic prophylaxis during the puerperium to help prevent the majority of thromboses that can occur during this period. One hundred and fifty-eight women with a score of < 3 were spared 9 months of LMWH prophylaxis and 153 others with a score of 3–5 were spared 6 months of LMWH prophylaxis, respectively, with

0.37% of antepartum-related VTEs and 0.37% of bleeds. The results suggest the efficacy and safety of treatment provided by use of the Lyon VTE score. The use of such tools offers the prospect of personalized medicine, which is more effective and probably more cost-efficient than 'inclusive, equal treatment for all'. This last point, as well as the value of individualization of care in the postpartum period, needs to be confirmed in future studies.

Addendum

Y. Dargaud designed the study, performed the research, recruited the patients, interpreted results, and wrote the manuscript. C. Fleury was responsible for collection and assembly of data. L. Rugeri performed the research, recruited the patients, and critically revised the manuscript. C. Battie, P. Gaucherand, C. Huissoud, R. C. Rudigoz, H. Desmurs Clavel, and J. Ninet recruited the patients. M. C. Trzeciak designed the study and gave final approval of the manuscript. All authors approved the final draft.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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