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A risk score for the management of pregnant women with increased risk of venous thromboembolism: a multicentre prospective study

Yesim Dargaud,[1,2] Lucia Rugeri,[1] Marie Christine Vergnes,[3] Brigitte Arnuti,[4] Paula Miranda,[5] Claude Negrier,[1,2] Audrey Bestion,[6] Hélène Desmurs-Clavel,[7] Jacques Ninet,[7] Pascal Gaucherand,[8] Rene Charles Rudigoz,[9] Michel Berland,[10] Fabienne Champion[11] and Marie Christine Trzeciak[1]

[1]Unité d'Hémostase Clinique, Hôpital Edouard Herriot, [2]EA 4174, IFR 62, Université Lyon 1, Lyon, [3]Laboratoire d'Hémobiologie, CHU de Bordeaux, Pessac, [4]Service d'Hémostase et d'Hémovigilance, CH de Valence, [5]Service de Médecine interne, CH de Roanne, [6]Pôle Information Médicale, Evaluation statistique & Recherche, [7]Service de Médecine Interne, Médecine Vasculaire, Hôpital Edouard Herriot, [8]Service d'Obstétrique, Hôpital Femmes Mères Enfants, [9]Service de Gynécologie Obstétrique, Hôpital de la Croix Rousse, [10]Service de Gynécologie Obstétrique, Centre Hospitalier Lyon Sud, and [11]Service de Gynécologie Obstétrique, Hôpital Hôtel Dieu, Lyon, France

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Correspondence: Yesim Dargaud, MD, PhD, Unite d'Hemostase Clinique, Hôpital Edouard Herriot Pavillon E, 5, place d'Arsonval, 69003 Lyon, France. E-mail: ydargaud@univ-lyon1.fr

Summary

Patients with thrombophilia and/or a history of venous thromboembolism (VTE) exhibit a high risk of thrombosis during pregnancy. The present multicentre study prospectively assessed a prophylaxis strategy, based on a risk score, in pregnancies with increased risk of VTE. Among 286 patients included in the study, 183 had a personal history of VTE (63·98%) and 191 patients (66·8%) had a thrombophilia marker. Eighty nine (46·6%) thrombophilic women had a personal history of VTE. Patients were assigned to one of three prophylaxis strategies according to the risk scoring system. In postpartum, all patients received low molecular weight heparin (LMWH) prophylaxis for at least 6 weeks. In antepartum, LMWH prophylaxis was prescribed to 61·8% of patients with high risk of VTE. Among them, 37·7% were treated in the third trimester only and 24·1% were treated throughout pregnancy. In this cohort, one antepartum-related VTE (0·35%) and two postpartum-related VTE (0·7%) occurred. No case of pulmonary embolism was observed during the study period. The rate of serious bleeding was 0·35%. There was no evidence of heparin-induced thrombocytopenia or osteoporosis. 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: pregnancy, venous thromboembolism, risk score, thrombophilia, thromboprophylaxis.

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a multicausal frequent disease that is associated with substantial morbidity and mortality. In pregnancy, the risk of VTE is 2- to 4-fold higher than in a non-pregnant woman of a similar age (Greer, 1999; Ginsberg & Bates, 2003). The risk is moderately increased during the first and second trimesters, and increases sharply during the third trimester and in puerperium (Ray & Chan, 1999; Ros *et al*, 2001; Heit *et al*, 2005). The risk of thrombosis increases even further if a patient has a predisposition to venous thrombosis (Robertson *et al*, 2005).

The high rate of postpartum-related VTE was significantly reduced with the use of antithrombotic prophylaxis on a large scale (Toglia & Weg, 1996). As a result, several recent studies strongly suggested that the majority of thromboembolic events occur in antepartum (Robertson & Greer, 2005). However, because of the low absolute risk of thrombosis in pregnant women with a tendency to VTE, systematic prophylaxis with

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low molecular weight heparin (LMWH) is not recommended for all pregnant women with thrombophilia (Bates *et al*, 2004; Krafft, 2007). In antepartum, the decision to administer thromboprophylaxis should be considered on an individual basis with regard to lowering the absolute risk of thrombosis, the inconvenience of daily subcutaneous heparin therapy and the potential risks of bleeding, heparin-induced thrombocytopenia (HIT) and osteoporosis (Howell *et al*, 1983; Casele *et al*, 2006). An individual assessment of the VTE risk is crucial for optimal thromboprophylaxis, but there is no validated tool to help clinicians to stratify VTE risk in pregnant women and to introduce prophylactic anticoagulation at the right time. Recommendations based on case-control studies and expert opinions do not entirely highlight the physicians' need and the management of VTE risk in pregnancy still remains a challenge. The use of a risk stratification tool that takes all individual risk factors for VTE into consideration and that aids the decision-making process of antenatal anti-thrombotic prophylaxis may be helpful for physicians dealing with these pregnancies.

Our group has previously described a VTE risk prediction score, rating patients at increased risk of VTE and recommending individually adapted management (Dargaud *et al*, 2005). A retrospective evaluation of the initial score showed favourable outcomes in pregnancies with high risk of thrombosis (Dargaud *et al*, 2005). In the present study, a modified version of this score and related management strategy was prospectively assessed in a multicentre clinical trial.

Materials and methods

Patients

Between January 2005 and September 2007, 342 consecutive pregnant women, who were referred with a diagnosis of confirmed thrombophilia and/or a personal history of VTE, were enrolled at four centres in France [(i) Department of Clinical Haemostasis, Department of Internal Medicine & Vascular Medicine, all Departments of Gynecology & Obstetrics in Lyon University Hospitals; (ii) Haemobiology Laboratory, Cardiologic Hospital, Bordeaux; (iii) Department of Internal Medicine, CH de Roanne; (iv) Department of Haemostasis and Haemovigilance, CH de Valence]. Most patients were recruited after referral by another physician.

Exclusion criteria included (i) contraindications to heparin therapy, (ii) patients with obstetric complications only (such as recurrent miscarriages, pre-eclampsia, HELLP (haemolysis, elevated liver enzyme, low platelet count) syndrome, intrauterine growth restriction) and (iii) patients with superficial venous thromboses only, (iv) patients with highest VTE risk (antiphospholipid syndrome, antithrombin deficiency and women receiving long-term anticoagulants) for whom clear recommendations with a high level of evidence were available. These last ones were treated according to the international recommendations published in 2004 (Bates *et al*, 2004) and recently updated in 2008 by the American College of Chest Physicians (ACCP) (Bates *et al*, 2008).

Pregnant women with high and moderate risk of VTE because of a prior VTE and/or common thrombophilia marker(s), for whom recommendations propose different possibilities of management, were included in the present study after obtaining informed consent. All patients included in the study underwent a standardized interview on their VTE risk using a concise questionnaire.

Thrombophilia testing

Peripheral venous blood was collected into Vacutainer® tubes (Becton Dickinson, Meylan, France) containing 0·129mol/l trisodium citrate (one volume trisodium citrate to nine volumes blood) from antecubital venipuncture. Following a double centrifugation at 2500 ***g*** for 15 min, platelet poor plasma was collected, quick-frozen and stored at −80°C. Thrombophilia tests included cell blood count, coagulation assays (activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time, fibrinogen), antithrombin (AT), protein C (PC) activity, protein S (PS) activity and free PS antigen, activated protein C (APC) resistance, lupus anticoagulant, anticardiolipin antibodies, *F5* G1691A (factor V Leiden) and *F2* G20210A mutations.

Antithrombin activity was detected by an automated amidolytic assay (Coamatic Antithrombin®, Chromogenix, Milan, Italy). PC activity was measured by two automated tests: an amidolytic assay using Coamatic Protein C® (Chromogenix, Milan, Italy) and a clotting assay (Staclot- Protein C, Diagnostica Stago, Asnières sur Seine, France). Free PS antigen was measured by an enzyme-linked immunosorbent assay (ELISA) method (Asserachrom Protein S Free, Diagnostica Stago, Asnières sur Seine, France). PS activity was detected by a clotting assay (Staclot Protein S, Diagnostica Stago, Asnières sur Seine, France). Screening for PS deficiency was performed in women with no oral contraceptive use and before falling pregnant or delayed until 12 weeks postpartum. The first generation APC resistance assay was performed as previously described (Koster *et al*, 1993). Lupus anticoagulant assays were performed using aPTT and dilute Russell's viper venom time (DRVVT) according to the recommendations of the International Society of Thrombosis and Haemostasis (ISTH) scientific subcommittee (Exner, 1995). Anticardiolipin antibodies (IgM and IgG), anti-beta 2 glycoprotein I (β_2-GPI) antibodies were tested by ELISA and results were interpreted according to the updated criteria recently published by the ISTH scientific subcommittee (Miyakis *et al*, 2006). D-dimer levels (VIDAS, Biomérieux, Marcy l'Etoile, France) were determined by ELISA. *F5* G1691A and *F2* G20210A mutations were detected using a multiplex polymerase chain reaction (PCR) – directed mutagenesis protocol as previously described (Ripoll & Paulin Thomas, 1997). All laboratory diagnoses, except genetic abnormalities, were confirmed by a second measurement performed at least one month after the first determination.

VTE risk score

The score assessed VTE risk during pregancy using three main criteria, (i) personal history of VTE, (ii) known thrombophilia markers and (iii) contemporary risk factors dependent on the ongoing 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 I).

Personal history of VTE. In patients with prior VTE, the very-high-risk group (six points) comprised patients with a personal history of very serious or unusual thrombotic episodes, such as massive PE with hypotension and cardiogenic shock or cerebral venous thrombosis (CVT) or spontaneous VTE during childhood, and also women with a personal history of pregnancy-related VTE (Pabinger *et al*, 2002; Robertson *et al*, 2005). It was previously demonstrated that patients exhibiting VTE during pregnancy had a significantly increased risk of future pregnancy-related recurrent thrombosis (Robertson *et al*, 2005).

With regard to DVT and PE history, the risk score was balanced according to the seriousness of the thrombotic event. The presence of transient risk factors in the month preceding VTE was recorded and included surgery, trauma, leg cast or prolonged bed immobilisation (>4 d). If none of the aforementioned conditions were present, VTE was considered spontaneous. The lowest risk (one point) was assigned to distal calf DVT with transient risk factors. An intermediate risk (two points) was assigned to spontaneous calf DVT or proximal VTE with transient risk factor and finally, a higher risk (three points) was assigned to spontaneous or oestrogen-related proximal DVT or PE. According to the recent ACCP recommendations (Bates *et al*, 2004, 2008), the score assigned a higher recurrence risk to oestrogen-related VTE. It has been previously shown that recurrence rates are significantly influenced by clinical risk factors at the time of the first event. The recurrence rate was significantly lower in patients with a trigger at the time of their first VTE event in comparison with patients with unprecipitated VTE (Baglin *et al*, 2003). In patients with a calf DVT, a low recurrence rate was shown after 6 weeks of oral anticoagulation (Astermark *et al*, 1998; Pinede *et al*, 2001) and the clinical relevance of distal DVT is still debated (Righini & Bounameaux, 2008). In the present study, the low thrombotic risk assigned to distal DVTs and venous thromboses with transient risk factors is in line with previously reported data (Pinede *et al*, 2001; Righini & Bounameaux, 2008).

The score also took into account other DVT recurrence risk factors e.g. personal history of recurrent VTE (Schulman & Ogren, 2006), presence of residual thrombi objectively detected by compression ultrasound (CUS) (Prandoni *et al*, 2002; Young *et al*, 2006) and history of recent VTE which occurred <2 years before (Janssen *et al*, 1987). It has been previously demonstrated that the VTE recurrence risk is significantly higher in this period (Janssen *et al*, 1987). Several studies also showed that the risk of recurrent venous

Table I. Score for the assessment of the risk of pregnancy- related venous thromboembolism and corresponding prophylaxis strategy.

Personal history of VTE	History of VTE related to pregnancy (occurred during the antepartum), or CVT or massive PE or VTE in childhood (<16 y.o.)	6
	Spontaneous or oestrogen induced PE or proximal DVT	3
	Transient risk factor induced PE or proximal DVT	2
	Spontaneous or oestrogen induced distal calf DVT	2
	Transient risk factor induced distal calf DVT	1
If there's a personal history of VTE	Recurrent VTE history	3
	Residual venous thrombi	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, immobilisation	2
	Twin pregnancy	1
	Age > 35 years	1
	Body Mass Index > 30	1
Total score=		.....
No. antenatal prophylaxis if score <3.		
Early heparin prophylaxis in patients with a score ≥6		
LMWH was prescribed only in the third trimester to patients with a score between 3 and 5.		

VTE, venous thromboembolism; CVT, Cerebral venous thrombosis; PE, pulmonary embolism; DVT, deep vein thrombosis.

thromboembolism is higher in patients with residual thrombi than in those without (Prandoni *et al*, 2002; Agnelli & Becattini, 2008). Bilateral, comparative colour duplex venous ultrasound was carried out by senior vascular physicians in patients who did not have an objective evalution of post-thrombotic sequelae at anticoagulant withdrawal. The aim of the ultrasound exam was to detect post-thrombotic sequelae in women with a history of DVT. The presence of residual venous thrombus was determined according to the method of Prandoni *et al* (2002). Briefly, vein compression was performed in the transverse plane and vein diameter was measured in millimetres during maximal compression. Residual obstruction was defined as present if the vein transverse diameter was >2 mm at maximal compression. There was no systematic evaluation of superficial venous insufficiency.

Thrombophilia. Known thrombophilic defects were recorded and thrombophilia testing was performed in patients who did not have a thrombophilia screening before pregnancy. In patients presenting a thrombophilia marker, the highest risk was assigned to combined thrombophilia risk factors and homozygous mutations, according to the previous data showing that women with these abnormalities may need to be managed through a more aggressive process than those with other heritable thrombophilias (Gerhardt *et al*, 2000; Martinelli *et al*, 2001; Samama *et al*, 2003). A mild risk (one point) was assigned to other thrombophilia risk factors i.e. PC or PS deficiencies, heterozygous *F5* G1691A or *F2* G20210A mutations. This risk stratification is in accordance with previously reported data showing a risk of VTE at 1:437 for women with *F5* G1691A mutation, 1:113 for women with PC deficiency and 1:200 for those with the *F2* G20210A mutation (Bates, 2007). Significantly higher risk of VTE (1:2·8) was reported for double heterozygotes (4·6:100) (Bates, 2007). In patients with no detected thrombophilia, the score assigned a mild risk (one point) to a significant family history of VTE, defined as unprovoked or pregnancy-related or oestrogen-related VTE and/or recurrent thromboses in the first-degree family members (parents or siblings) (Noboa *et al*, 2008).

Contemporary risk factors. Finally, the score also took into consideration individual risk factors and risks related to the ongoing pregnancy, such as age >35 years. (Macklon & Greer, 1996; James *et al*, 2006), obesity (body mass index, BMI > 30) (Larsen *et al*, 2005; Jacobsen *et al*, 2008), prolonged immobilisation during pregnancy (Lindqvist *et al*, 1999; Danilenko-Dixon *et al*, 2001; Simpson *et al*, 2001) or twin pregnancy (Lindqvist *et al*, 1999; Simpson *et al*, 2001). Prolonged immobilisation during pregnancy was defined as a bed rest lasting more than 4 d (Alikhan *et al*, 2004), an orthopaedic immobilisation (cast or brace) (Ettema *et al*, 2008) or air travel for longer than 8 h (Schreijer *et al*, 2006).

Individually tailored antenatal management of VTE risk using the risk score

In antepartum, class II elastic stockings were systematically prescribed to all patients. According to the VTE risk level evaluated with this score in early pregnancy, an antenatal thromboprophylaxis by LMWH was immediately prescribed to patients presenting a very high VTE risk with a score ≥6. Thromboprophylaxis was prescribed only in the third trimester to patients presenting a high risk of VTE with a score of 3–5. No antenatal LMWH prophylaxis was prescribed in patients with a score <3. LMWH prophylaxis used in the study was enoxaparin 40 mg SC q24h (Lepercq *et al*, 2001) except in patients with morbid obesity (BMI > 35) who received an intermediate dose of enoxaparin 60 mg SC q24h (Lebaudy *et al*, 2008; Simione *et al*, 2008).

Patients were seen at monthly intervals for a clinical examination that included assessment of leg tenderness, leg oedema and localized pressure-pain. VTE risk was evaluated monthly and LMWH prophylaxis was started immediately if the score became ≥6 at any time during the pregnancy. Long term bed rest, immobilisation and surgery were the main risk factors searched for during pregnancy.

In postpartum, LMWH prophylaxis was prescribed to all patients in association with class II elastic stockings. It has been previously shown that operative delivery increases the risk of postpartum-related VTE (Ros *et al*, 2002). In this study, LMWH was given for 6 weeks to patients who had a vaginal delivery and for 8 weeks to women who delivered by Caesarean section. Patients were advised not to use oestroprogestative pills as the method of contraception after birth.

Efficacy and safety assessments

The efficacy outcome was the incidence of symptomatic DVT objectively confirmed by CUS or PE confirmed by helical computed tomography or ventilation-perfusion scintigraphy.

The main safety outcomes were bleeding, HIT, symptomatic osteoporosis and serious urticarial rash related to heparin therapy. A diagnosis of HIT was based on platelet aggregation tests and on testing for heparin-platelet factor 4 antibodies. Osteoporosis was defined as the occurrence of clinical signs of osteoporosis and/or osteoporotic fractures. Full term pregnancy was defined as a delivery that occurred at 40 ± 2 gestational weeks. All the episodes of VTE and safety outcomes that occurred during pregnancy were recorded. The puerperium was defined as the period from childbirth to the first 8 weeks postpartum.

A late postpartum visit was systematically performed for all patients, 12 weeks after delivery, where all puerperium-related efficacy and safety outcomes were recorded.

Statistical analysis

Data were expressed as mean ± standard deviation or percentages and 95% confidence intervals (CIs) were

calculated using the normal approximation to the binomial distribution. Statistical analysis was performed using the GRAPHPAD INSTAT 3.0_ software package (San Diego, CA, USA).

Results

Description of the study patients

A total of 342 pregnant women with high risk of VTE were enrolled in the study. Fifty six patients had one or more of the exclusion criteria and were ineligible for the study for the following reasons: one patient due to antithrombin deficiency and a prior DVT, six patients had a known antiphospholipid syndrome and personal history of VTE, three women required long term anticoagulation therapy, 27 patients had thrombophilia markers and prior recurrent miscarriages and 17 women had thrombophilia markers and preeclampsia or HELLP syndrome or intrauterine growth restriction. Thus, 288 women met the eligibility criteria. Of these, two were unable to return for follow-up. A total of 286 patients were entered into the trial. The mean age (±SD) was 31 (±4·9) years and the mean BMI was 24 (±4·4). Fifty three patients were aged >35 years. There were 29 obese patients with a BMI ≥30, 40 smokers and seven twin pregnancies. 130 patients were primiparous and 155 multiparous. Eleven patients had been immobilized over a long period previous to delivery and one woman had experienced pregnancy toxaemia during the ongoing pregnancy. Among, 286 patients, 183 had a personal history of VTE (63·98%), of whom 27·9% had proximal DVT, 43·3% distal calf DVT, 18·3% PE, 3% CVT, 6·56% recurrent VTE and 14·2% had a residual thrombus detected by CUS. Among 26 women with post-thrombotic sequelae, only one patient had residual thrombi of a peroneal vein, whilst 25 others exhibited residual thrombi of proximal veins. Laboratory tests showed thrombophilia markers in 192 patients (67·1%). Eighty nine (46·6%) thrombophilic women had a personal history of VTE. Proximal DVT was 1·2 times more frequent in the group of patients presenting a thrombophilia marker. Table II shows the baseline characteristics and the distribution of VTE episodes in the thrombophilia groups.

Antenatal and postnatal management of the thrombotic risk

Of the 286 pregnancies at high risk of VTE, LMWH prophylaxis, e.g., enoxaparin, was prescribed in 177 cases (61·8%) with a positive risk score (≥3). One hundred and seventy four of them had enoxaparin 40 mg SC q24h and three patients with morbid obesity (BMI > 35) had intermediate doses (60 mg q24h). Among these patients, 108 (37·7%) were treated during the third trimester because of a high risk of VTE (score = 3–5) and 69 patients (24·1%) were treated earlier because of a very high risk of thrombosis (score ≥ 6). In the group of 109 patients (38·1%) with a moderate risk score <3, no patients received LMWH prophylaxis in antepartum (Table III).

All patients included in the study were treated with class II elastic stockings except five women who did not comply with their assigned compression. All patients had a routine follow-up involving monthly visits. The risk of VTE was re-evaluated every month and LMWH prophylaxis was introduced earlier than expected in 11 cases of long-term bed rest related to a preterm delivery risk.

Among 286 pregnancies, 56 women underwent a Caesarean section and 230 had a vaginal delivery. In post partum, LMWH

Table II. VTE history in patients with thrombophilia.

Confirmed thrombophilia	*n*	PE	Proximal DVT	Distal DVT	CVT	Recurrent VTE
Protein C deficiency	14	0	3	5	1	1
Protein S deficiency	17	2	7	3	0	0
F5 G1691A heterozygous	99	3	17	18	0	0
F2 G20210A heterozygous	39	6	7	6	3	2
APC resistance	3	1	0	1	0	0
FV Leiden homozygous	4	1	0	1	0	0
F2 G20210A homozygous	1	1	0	0	0	0
PC deficiency homozygous	1	0	0	0	0	0
Combined *F5*G1691A + *F2*G20210A	8	0	1	2	0	1
Combined *F5*G1691A + PS deficiency	3	0	0	1	0	0
Combined *F5* G1691A + C deficiency	1	0	0	0	0	0
F2 G20210A + PC deficiency	1	0	0	0	0	0
F2 G20210A + PS deficiency	1	0	0	0	0	0
No known thrombophilia	94	19	29	45	3	8
Total	286	33	64	82	4	12

VTE, venous thromboembolism; CVT, Cerebral venous thrombosis; PE, pulmonary embolism; DVT, deep vein thrombosis.

Table III. VTE risk stratification in the study population, treatment strategy and main efficacy & safety outcomes.

	Score < 3	Score = 3–5	Score ≥ 6
Score and prophylaxis strategy	No LMWH prophylaxis in antepartum; LMWH at least 6 weeks in postpartum	LMWH prophylaxis at the third trimester; LMWH at least 6 weeks in postpartum	LMWH prophylaxis throughout pregnancy; LMWH at least 6 weeks in postpartum
Number of cases, *n = 286*	109	108	69
Personal history of VTE n = 183	25 (23%)	89 (82·4%)	69 (100%)
VTE related to pregnancy or CVT or massive PE or VTE in childhood	0	0	34
Spontaneous or oestrogen-induced PE or proximal DVT	1	28	16
Transient risk factor-induced PE or proximal DVT	2	21	8
Spontaneous or oestrogen-induced calf DVT	5	21	6
Transient risk factor-induced calf DVT	17	19	5
Recurrent VTE	0	2	10
Residual thrombi	0	5	21
Inherited thrombophilia *n = 192*	88 (80·7%)	68 (62·9%)	36 (52·2%)
LMWH prophylaxis given according to the results of the score	109	108	69
VTE occurred during antepartum	1	0	0
VTE occurred during puerperium	0	1	1
Postpartum haemorrhage	1	0	0

VTE, venous thromboembolism; CVT, Cerebral venous thrombosis; PE, pulmonary embolism; DVT, deep vein thrombosis; LMWH, low molecular weight heparin.

was given for 6 weeks in 230 patients that had a vaginal delivery and for 8 weeks in 56 women who delivered by Caesarean section.

Efficacy outcomes

During the study period, three women experienced a DVT (Table IV). Two DVT episodes occurred in the postpartum period few days after LMWH therapy withdrawal (0·7%; 95% CI = 0–1·67%). The first patient was a 40-year-old obese woman (BMI = 36·7) who was heterozygous for the *F5* G1691A mutation and had a personal history of idiopathic muscular calf DVT. She had enoxaparin 60 mg q24h in the third trimester and for 6 weeks after vaginal delivery and presented a new episode of DVT in the seventh week postpartum, 5 d after LMWH withdrawal.

The second patient was a 33-year-old woman with a history of spontaneous proximal DVT and significant post-thrombotic sequels. She was heterozygous for the *F5* G1691A mutation. She had enoxaparin 40 mg q24h throughout pregnancy and for 6 weeks after vaginal delivery. She experienced a DVT at day 49, 6 d after LMWH withdrawal.

One antepartum-related DVT occurred (0·35%; 95% CI = 0–1·03%). The patient was a 29-year-old lady with no history of VTE but was referred to us for a heterozygous *F5* G1691A mutation. She experienced a proximal DVT of the left leg related to frequent bed-resting in the eighth month of pregnancy. The clinician did not introduce LMWH prophylaxis to this patient who did not require continuous bed rest.

We also recorded a catheter-related superficial vein thrombosis, in a 39-year-old patient, despite LMWH prophylaxis. Upper limb superficial vein thrombosis occurred following an amniocentesis with a difficult placement of a venous catheter.

Safety outcomes

Only one patient undergoing induced labour had a serious postpartum haemorrhage and she was not receiving heparin at the time of this event. No HIT was detected during the study period. No symptomatic osteoporosis occurred in the present series. Two patients experienced moderate urticarial rash related to enoxaparin therapy. Allergic symptoms disappeared after enoxaparin withdrawal followed by the introduction of another LMWH.

Table IV. Thromboembolic events.

Patient characteristics	Score	VTE prophylaxis	Event	Period
Patient 1 40 years old BMI 36·7 History of spontaneous muscular calf vein thrombosis Heterozygous *F5* G1691A Vaginal delivery	5	Enoxaparin 60 mg q24h in the third trimester and in postpartum until 6 weeks + elastic stockings	Calf DVT	Post partum seventh week
Patient 2 33 years old BMI 19 History of spontaneous proximal DVT Post thrombotic sequels (residual thrombi) Heterozygous *F5* G1691A Vaginal delivery	7	Enoxaparin 40 mg q24h throughout pregnancy and in postpartum until 6 weeks + elastic stockings	Calf DVT	Post partum seventh week
Patient 3 29 years old BMI 26 No history of VTE Heterozygous *F5* G1691A	1	Elastic stockings no heparin prophylaxis in antepartum	Proximal DVT (bed resting)	Pregnancy eighth month

DVT, deep vein thrombosis; BMI, body mass index.

Discussion

The risk score assessed in the present study is derived from our previously published score (Dargaud *et al*, 2005). The main difference between the initial score and the present version is the exclusion of patients for whom high grade recommendations are available (e.g. antiphospholipid syndrome, women receiving long term anticoagulants and AT deficiency). These patients were excluded and treated according to the recommendations published by the ACCP (Bates *et al*, 2004, 2008). Another difference is related to data on residual thrombi, which was systematically explored in this prospective study but was not available for all patients in the first retrospective study.

The score was applied to 286 patients for whom ACCP recommendations suggest different antenatal management possibilities i.e. prophylactic LMWH, intermediate dose LMWH/unfractionated heparin or clinical surveillance throughout pregnancy. Our results demonstrated an excellent clinical applicability of the score in four participating centres because all women included in the study had an individualized management according to the results of the score.

The incidence of VTE during pregnancy was reported to be about 1:1000 in healthy pregnant women (Gris *et al*, 2006) and the risk is higher during pregnancy in patients with inherited thrombophilia and in those with a history of VTE. For example, in asymptomatic *F5* G1691A carriers, this risk is estimated at 1:400 (McColl *et al*, 1997) and is dramatically higher (1:3) in pregnant women with asymptomatic type 1 antithrombin deficiency (Gris *et al*, 2006). In the present study, where patients with APL syndrome or AT deficiency were excluded, a 5–6% recurrence was expected without LMWH prophylaxis (Ray & Chan, 1999; Brill Edwards *et al*, 2000; De Stefano *et al*, 2006). A risk of recurrence of below 2% was previously reported in patients with heparin prophylaxis (Sanson *et al*, 1999). In this cohort, one antepartum-related VTE (0·35%; 95% CI = 0–1·03%) occurred. It was a patient with *F5* G1691A mutation who experienced a proximal DVT during frequent bed resting. The patient had no complete bed rest, but she was advised to frequently rest in bed to limit mild uterine contractions. Prolonged bed rest is a frequent risk factor of VTE in pregnant women but needs to be defined precisely. In our study, LMWH therapy was started earlier in eleven patients because of a prolonged bed-rest (>4 d) related to the risk of preterm labour but, in this particular patient, the physician did not prescribe thrombophylaxis because the patient had no strict bed rest.

This score was designed to assess the individual thrombosis risk during antepartum and to tailor heparin prophylaxis during this period. The results of this prospective multicentre study suggest that the use of the present risk score may effectively reduce the rate of antepartum related thrombotic events in women with high risk of VTE (Cohen *et al*, 2005, 2006).

Thromboprophylaxis is strongly recommended in postpartum because of the higher average daily risk of VTE in the postpartum period (Gherman *et al*, 1999; Ray & Chan, 1999; Martinelli *et al*, 2007). Several studies showed that the risk of VTE was particularly high during the first 6 weeks postpartum (Greer & Nelson-Piercy, 2005). Therefore, LMWH prophylaxis was systematically prescribed for 6 weeks postpartum in these patients with high risk of VTE. Available data suggests that the risk of VTE is higher after Caesarean section than after vaginal

delivery (Greer, 1999); for that reason, prophylaxis for 8 weeks postpartum was chosen for women who delivered by Caesarean section. In our study, two postpartum-related VTE (0·7%; 95% CI = 0·67%) occurred. No case of PE was described during the study period. These two patients experienced a calf DVT at week 7 after delivery, a few days after heparin withdrawal. These two patients presenting several thrombosis risk factors delivered vaginally and had LMWH prophylaxis for 6 weeks postpartum. Our results are in line with the results of several prospective and retrospective studies reporting that postpartum-related VTE may occur despite standard prophylaxis (Pabinger *et al*, 2005; Gris *et al*, 2006). These results open up debate about the need for an individually tailored prophylaxis not only in antepartum but also in the postpartum period.

Only one patient (with no heparin prophylaxis) experienced a serious postpartum haemorrhage (0·35%). This low bleeding rate was similar to the available safety data of LMWH thromboprophylaxis in pregnancy (0·43%; 95% CI = 0·22–0·75) (Greer & Nelson-Piercy, 2005; Pomp *et al*, 2008). No cases of HIT or clinically relevant osteoporosis were observed. Two cases of urticarial rash were successfully controlled by switching enoxaparin prophylaxis to tinzaparin 4500 U/d. Our results showed a satisfactory safety profile for this score-based management strategy.

Chauleur *et al* (2008) reported an easy-to-use risk score designed for the screening and management of VTE risk in pregnant women. This prospective study included 2736 pregnant women. Among them, 1% had a previous VTE and 0·7% exhibited a congenital thrombophilia. 2685 women received the recommended treatment defined by the risk score and nine pregnancy-related VTE occurred during the study period (Chauleur *et al*, 2008; Dargaud *et al*, 2008).

Recently, Bauersachs *et al* (2007) reported another risk stratification tool for women with a history of VTE, thrombophilia or both. In their prospective multicenter study, patients were assigned to one of three risk groups i.e. low, high or very high risk patients. As a result, 72% of patients had LMWH therapy throughout pregnancy and for 6 weeks postpartum with a symptomatic VTE rate of 0·6% and a clinically relevant bleeding rate of 4·6% (Bauersachs *et al* 2007). In our study, antepartum LMWH prophylaxis was prescribed in 61·8% of cases. Among them, 37·7% were treated at the third trimester only and 24·1% were treated earlier. The ''right'' time to introduce antepartum LMWH prophylaxis is not known and there is no strong evidence supporting the necessity for heparin therapy for the full 40 weeks during pregnancy. It has been shown that the risk was highest in the third trimester of pregnancy (Simpson *et al*, 2001) and fatal PE was more frequent in the third trimester and postpartum (James *et al*, 2006). On the basis of this finding, in patients with moderate risk of VTE (score = 3–5), we prescribed heparin prophylaxis in the third trimester. No thrombosis occurred in this group suggesting that in some cases, the use of our risk score may effectively and safely limit the duration of heparin therapy. In addition, in this group, the use of LMWH prophylaxis in the third trimester only lead to a reduction of the cost of LMWH therapy by 1·6 with equivalent efficacy and safety.

The score-based management strategy described in this study is in accordance with the ACCP recommendations (Bates *et al*, 2008). This multi-parametric approach, taking into account not only the VTE history and thrombophilia markers but also other VTE risk factors, is original and may better reflect the clinical VTE risk of patients in comparison with other risk stratification tools available in the literature.

The present pilot study has several limitations. The population size is limited. Most of the risk factors of VTE recurrence used in this score have been described in the general population including males and females, and specific data for pregnant women is scarce. In addition, most of the VTE risk factors have been studied in the context of proximal VTE and there is only limited data available on distal venous thromboses. This cohort study including pregnant women at risk of thrombosis (i.e. women with known thrombophilia and/or a personal history of VTE) was non-randomized. A randomization procedure was not performed because it would be unethical to withhold heparin therapy from some patients at high risk of VTE. Therefore, the possibility of bias can not be completely excluded. Obviously, this prophylatic strategy based on a risk score cannot cover all clinical situations. In some difficult clinical cases, the empirical judgment of senior doctors remains essential. However, the routine use of a formal score may offer a rational risk assessment and prophylaxis approach in pregnancies with high risk of VTE. The present multicentre study included haematologists, obstetricians and internists and showed a good feasibility of the scoring system. A future randomized study is planned to compare the management strategy based on the risk score and the prophylaxis strategy empirically decided by an expert.

The decision to prescribe antepartum heparin prophylaxis should be individually decided in each pregnant woman with high risk of VTE. The use of a risk score may provide a rational decision process. The results of the present prospective, multicentre study confirmed our previous retrospective data and demonstrated the clinical applicability of this scoring system. Our results showed that the risk score presented here may be a helpful tool for the clinical management of pregnancies at high risk of VTE. Further studies with larger cohorts are required to confirm the results of this study.

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