International Journal of Gynecology and Obstetrics (2005) **90**, 203—207

International Journal of
GYNECOLOGY
& OBSTETRICS

www.elsevier.com/locate/ijgo

CLINICAL ARTICLE

Management of pregnant women with increased risk of venous thrombosis

Y. Dargaud [a,c,*], L. Rugeri [a], J. Ninet [b,c], C. Negrier [a], M.C. Trzeciak [a]

[a] *Laboratoire d'Hémostase et Unité d'Hémostase Clinique, Hôpital Edouard Herriot, Lyon, France*
[b] *Service de Médecine Interne, Hôpital Edouard Herriot, Lyon, France*
[c] *Service d'Angiologie - Explorations Vasculaires, Hôpital Edouard Herriot, Lyon, France*

Received 14 February 2005; accepted 13 May 2005

KEYWORDS
Venous thromboembolism;
Pregnancy;
Risk score;
Antithrombotic prophylaxis;
Low molecular weight heparin;
Thrombophilia

Abstract

Objective: To evaluate the usefulness of score based management of pregnancies with high risk of venous thromboembolism (VTE). *Method:* 116 consecutive pregnancies in 109 women with confirmed thrombophilia and/or history of VTE were studied. Patients were managed in accordance with international recommendations. Recently, a VTE risk prediction score was established. An independent group assessed retrospectively and in a blinded way the usefulness of this score. *Results:* Of the 116 pregnancies, an antithrombotic prophylaxis by low molecular weight heparin was prescribed in 61 cases (52.6%). All patients with a positive score ($n = 57$, 49.1%) have been treated with an antenatal thromboprophylaxis. In the population where the score was negative ($n = 55$ cases), none of the patients received antenatal prophylaxis. But, despite a negative score, four patients were treated by their general practitioner. During the study period, there was only one episode of VTE. *Conclusion:* Implementing this scoring system has resulted in favorable outcomes and a low risk of recurrent thrombosis in this limited series of women with increased risk of VTE.

1. Introduction

Pregnancy is a risk factor for venous thromboembolism (VTE). VTE incidence during pregnancy is estimated at 1 per 1000 [1] and is 10 times higher in the postpartum period [2]. VTE is a multicausal disease resulting from combined effects of congen-

* Corresponding author. Laboratoire d'Hémostase pav. E, Hôpital Edouard Herriot, 5, place d' Arsonval, 69003 Lyon, France. Tel.: +33 4 72 11 73 70; fax: +33 4 72 11 73 12.
E-mail address: ydargaud@univ-lyon1.fr (Y. Dargaud).

0020-7292/$ - see front matter © 2005 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd.
doi:10.1016/j.ijgo.2005.05.003

ital and acquired risk factors. Thus, pregnant women presenting thrombophilia markers are predisposed to thrombotic complications responsible for maternal and foetal morbidity and mortality. Recommended use of antithrombotic agents during pregnancy has been published by Bates et al. [3]. According to these recommendations (grade 2C), patients with single episode of idiopathic VTE or thrombophilia (except antithrombin (AT) deficiency, combined heterozygous factor II and V Leiden mutations and homozygotes for these conditions) might receive mini-dose unfractionated heparin (UFH) or moderate-dose UFH or prophylactic low molecular weight heparin (LMWH) or clinical surveillance, plus postpartum anticoagulants. As such there is no standardized management protocol and the antepartum prophylaxis decision is often the responsibility of physicians. Heparin prescription to pregnant women with thrombophilia is arbitrary.

A VTE risk prediction rule rating patients at increased risk of VTE and recommending treatment management was established. This score concerns patients for whom recommendations propose different possibilities of management. Cases with detailed recommendations were treated according to international recommendations and were not included in this study.

An independent group conducted retrospective, blind assessment of the decision tree relating to thromboprophylaxis. Some 116 pregancies with an evaluated risk of VTE were reviewed.

2. Materials and methods

2.1. Patients

Records of 116 consecutive pregnancies in 109 women, who were referred to Lyon thrombosis centre between 2001 — 2003 as a result of confirmed thrombophilia and/or history of VTE, were reviewed. Seven women had two consecutive pregnancies. The mean age (±SD) was 34 (±4.88). Among 109 patients, 81 had a personal history of VTE (74.3%), of whom 32 had distal calf deep vein thrombosis (DVT) (29.3%), 28 proximal DVT (25.6%), 25 pulmonary embolism (22.9%), 3 cerebral vein thrombosis (2.75%) and 15 recurrent VTE (13.7%). Laboratory tests showed congenital or acquired thrombophilia markers in 59 women (54.3%). Thirty five (59.3%) thrombophilic women had a personal history of VTE. Table 1 shows the incidence of VTE in the thrombophilia groups in this series. During pregnancy monthly follow-up records were available for all patients. The records contained detailed medical history, physical examination reports, VTE history with precisions on the site (proximal or distal), type (spontaneous or with transient risk factor (TRF) or related to pregnancy), and severity of the thrombotic event (extensive DVT, pulmonary embolism). Full thrombophilia screening, including AT, protein C (PC) activity, protein S (PS) activity and free PS antigen, lupus anticoagulant, anticardiolipin antibodies, factor V Leiden and factor II G20210A mutations, was available to all patients. Thrombophilia screening was performed before pregnancy in most patients. AT deficiencies with personal VTE history, women receiving long term anticoagulation therapy and patients with known antiphospholipid syndrome and a history of VTE have not been included in this study as all required anticoagulation during the pregnancy and the puerperium according to the recommendations.

2.2. VTE risk score and antenatal management of the thrombotic risk

The score assessed VTE risk during pregnancy using 3 main criteria, personal history of VTE, previously

Table 1 Detailed distribution of venous thrombotic events regarding to the thrombophilia groups

Confirmed hypercoagulability	*n*	Distal DVT	Proximal DVT	PE	Cerebral vein thrombosis	Recurrent VTE
Antithrombin (AT) deficiency	1	0	0	0	0	0
Protein C (PC) deficiency	10	2	0	2	0	0
Protein S (PS) deficiency	3	1	1	1	0	1
Factor V Leiden (heterozygous)	27	7	7	1	0	2
FII G20210A (heterozygous)	9	0	5	2	0	0
Activated protein C resistance	1	0	0	1	0	0
Hyperhomocysteinemia (HH)	3	0	1	2	0	0
Combined AT+PC deficiency	1	0	0	0	0	0
Combined FV Leiden+G20210A	2	2	0	0	0	0
Combined FV Leiden+HH	2	0	0	0	1	1
No known thrombophilia	50	20	14	16	2	11
Total	109	32	28	25	3	15

DVT : deep vein thrombosis PE : pulmonary embolism VTE : venous thromboembolism.

Table 2 Venous thrombosis risk score

History of venous thrombosis	
□History of VTE related to pregnancy (occurred during the antepartum), or Cerebral VT or massive PE or VTE in childhood (<16 y.o.)	6
□Spontaneous PE or proximal DVT	3
□Transient risk factor induced PE or proximal DVT	2
□Spontaneous distal calf DVT	2
□Transient risk factor induced distal calf DVT	1
If history of venous thrombosis	
□Recurrent VTE history	3
□Residual venous thrombi	3
□Recent VTE history <2years	2
Confirmed hypercoagulability	
□Antithrombin deficiency, lupus anticoagulant, antiphospholipid antibody	6
□Combined thrombophilia risk factors	3
□Protein C deficiency, protein S deficiency, heterozygous FV Leiden mutation, heterozygous G20210A mutation	1
□If no hypercoagulability, family history of severe or recurrent VTE	1
Risk factors related to the current pregnancy	
□Bed resting, immobilisation	2
□Gemellary pregnancy	1
□Age >35 y.o	1
□Obesity with BMI >30	1
Total score	=.....

No antenatal thromboprophylaxis if the score<3. Heparin prophylaxis was immediately prescribed in patients presenting a score ≥6 and thromboprophylaxis was prescribed only in the 3rd trimester in patients with a score between 3 and 5.

known thrombophilia and contemporary risk factors dependent on the ongoing pregnancy (Table 2). According to the VTE risk level evaluated with this score in early pregnancy, an antenatal thromboprophylaxis by LMWH was immediately prescribed in patients presenting a score ≥6 and thromboprophylaxis was prescribed only in the 3rd trimester to patients with a score of 3—5. VTE risk was evaluated monthly and thromboprophylaxis was started if the score became ≥6 at any time during the pregnancy.

3. Results

The VTE risk score was retrospectively assessed. All patients with high risk of VTE were prescribed LMWH prophylaxis e.g. enoxaparin 40mg SC q24 h (Lovenox®, Sanofi-Aventis, Paris, France) for 6 to 8 weeks postpartum and compression stockings were given to all patients during the entire pregnancy.

Of the 116 pregnancies, an anti-thrombotic prophylaxis by prophylactic doses of LMWH e.g. enoxaparin 40mg SC q24 h, was prescribed in 61 cases (52.6%). All patients with a positive risk score (≥3) ($n=57$) were treated with an antenatal thromboprophylaxis. In spite of scoring <3, four patients were treated by their general practitioners in the 3rd trimester. Among the 61 patients who received antepartum prophylaxis, 44 (72.1%) were treated in the third trimester and 13 (21.3%) were treated earlier.

In the population where the score was <3 (55 cases), no patients received antenatal prophylaxis.

One case of VTE was recorded, a case of proximal DVT localised in the left superficial femoral vein diagnosed with compression ultrasound at 13 weeks gestation. She was referred to Lyon thrombosis centre after the diagnosis of DVT and was treated with adjusted-dose LMWH up to the 9th month and with adjusted-dose of UFH (during the last month).

No complication related to long term heparin therapy was noted, e.g. bleeding, heparin induced thrombocytopenia (H.I.T.), clinical sign of bone defect.

4. Discussion

This study investigated the management of pregnancies with high risk of VTE. Women with thrombophilia and/or prior VTE pose a challenge for future pregnancies because of the risk of vascular complications. All patients with a history of spontaneous VTE should be screened for a thrombophilia before pregnancy. Antenatal prophylaxis should be discussed for each individual taking into account all associated risk factors. This study assessed the usefulness of a risk score in the decision process for prophylactic treatment of pregnancies with high risk of VTE in a study group of 109 women.

In each category, only 1 point was assigned to the item presenting the lowest risk factor, the score was balanced for other items in accordance with the estimated risk degree available in the literature. In agreement with previous recommendations, the risk score assigned the highest risk (6 points) to patients exhibiting the presence of lupus anticoagulant and/or APL antibodies [3,4], and to patients presenting AT deficiency [5,6] and recommend an early antenatal antithrombotic prophylaxis in these individuals.

An intermediate risk (3 points) was assigned to patients with combined thrombophilia. There were only 2 double heterozygous carriers of both factor V Leiden and factor II gene mutation who had a

spontaneous DVT history. These patients benefited from a LMWH prophylaxis according to the results of Martinelli et al. [7] and Gerhardt et al. [8]. These works showed that the risk of DVT in women with both mutations was disproportionately higher than that in women with only one mutation. Samama et al. confirmed the necessity of prophylaxis in women with combined thrombophilia and a VTE history before pregnancy [9]. A mild risk (1 point) was assigned to other thrombophilia risk factors like PC or PS deficiencies, heterozygous FV Leiden mutation, heterozygous prothrombin gene mutation, hyper-homocysteinemia and isolated APC resistance. Factor V Leiden mutation is the most common thrombophilia risk factor in Europe, but the thrombotic risk for a women during pregnancy with FV Leiden is approximately 1 in 400—500. This low prevalence does not justify routine antepartum prophylaxis in women without prior VTE [10]. It has also been shown that during pregnancy, heterozygous prothrombin G20210A mutation represents a weak risk factor with respect to VTE [11]. In this study group, 7 of the nine women with G20210A mutation were treated with antenatal prophylaxis, but in these patients, LMWH was prescribed because of a previous history of severe VTE (pulmonary embolism, spontaneous or pregnancy related proximal DVT).

The second main criterion allowing a prescription of antenatal thromboprophylaxis is a personal history of VTE, since it has been shown that the history of thrombosis favors recurrent VTE [12]. This score also took into account the seriousness of the VTE history. The lowest risk (1 point) was assigned for distal DVT with transient risk factor, and the impact factor was balanced according to the conditions of the VTE histories. Thus, 2 points were assigned for spontaneous distal DVT, 3 points for spontaneous proximal DVT or spontaneous P.E. and the highest risk (6 points) was assigned for serious and unusual VTE history e.g. cerebral VT, massive PE, VTE in childhood, 6 points were also assigned for previous VTE related to pregnancy since it has been shown that patients exhibiting VTE during pregnancy had a significantly increased risk of future pregnancy-related DVT [12]. In these patients, prophylaxis was introduced early in pregnancy.

In patients with DVT history the score also takes into account DVT recurrence risk factors, e.g., presence of residual thrombi [13] and DVT history which occurred less than 2 years before, which as a rule is the time limit after which the tendency of the thrombosis-free survival curve after a first VTE decreases and it has been clearly shown that the recurrence risk is higher in this period [14]. The score also considered other risk factors, age, obesity, immobilization or bed rest during pregnancy [13] and gemellar pregnancies.

The American College of Chest Physicians (ACCP) have, published recommendations [3]. Experts emphasize the need for prophylaxis in compound heterozygotes for prothrombin G20210A and factor V Leiden and homozygotes for these conditions. But in cases with a single idiopathic episode of VTE or in patients with no prior VTE and thrombophilia, recommendations remain uncertain and different management possibilities have been suggested e.g. clinical surveillance, mini-dose UFH or prophylactic LMWH, plus postpartum anticoagulants (Grade 2C) [3]. The antenatal thromboprophylaxis strategy based on the risk score, assessed in this study, accords with these recommendations of the ACCP. Nevertheless, there are some specific differences. Unlike the ACCP recommendations, this system takes into account DVT recurrence risk factors, e.g., presence of residual thrombi, DVT history occurring 2 years previously. It also considers the seriousness of the VTE history and tries to tailor the length of the anticoagulant treatment in accordance with the estimated risk. Knowledge is lacking concerning the duration of antenatal thromboprophylaxis. The trimester of pregnancy to introduce thromboprophylaxis has not been studied and there is no evidence on the need for anticoagulant treatment for 40 weeks during pregnancy. A meta-analysis on the risk of VTE in different trimesters showed that fatal pulmonary embolism was more frequent in 3rd trimester and postpartum [15]. The VTE risk score took this into account, limiting the duration of anticoagulant therapy in women with moderate risk of thrombosis.

The retrospective character of the study constitutes its main limitation, but there are difficulties in performing prospective randomized studies in pregnant women.

In this series, the sub-group without heparin prophylaxis exhibited no thrombotic events during pregnancy or in puerperium. Of 116 followed pregnancies presenting an estimated risk of VTE only one case of DVT has been noted. The only case with VTE according to Table 2 had a score of 6 requiring an early antenatal prophylaxis but she was referred after the diagnosis of DVT. The score provides a rational decision process for antenatal anti-thrombotic prophylaxis, taking into account not only a confirmed hypercoagulable state, but also prior thrombosis history and risk factors related to the index pregnancy. In some cases it may help limit the number of women under heparin therapy (49.1% in this study). Further prospective multi-centre clinical trials with larger populations of pregnant women with high risk of VTE are

required to test the applicability of this scoring system.

References

[1] Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy : a population study. Obstet Gynecol 1999;94: 595–9.

[2] Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium : a meta-analysis of the period of risk and the leg of presentation. Obstet Gynecol Surv 1999;54: 265–71.

[3] Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy. The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:627S–44S.

[4] Empson M, Lassere M, Craig JC, Scott JR. Recurrent pregnancy loss with antiphospholipid antibody : a systematic review of therapeutic trials. Obstet Gynecol 2002;99: 135–44.

[5] Conard J, Horellou MH, Van Dreden P, Lecompte T, Samama M. Thrombosis and pregnancy in congenital deficiencies in AT III, protein C or protein S : study of 78 women. Thromb Haemost 1990;63:319–20.

[6] Ginsberg JS, Bates M. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1: 1435–42.

[7] Martinelli I, Legnani C, Bucciarelli P, Grandone E, De Stefano V, Mannucci PM. Risk of pregnancy related venous thrombosis in carriers of severe inherited thrombophilia. Thromb Haemost 2001;86:800–3.

[8] Gerhardt A, Scharf RE, Beckmann MW, Struve S, Bender HG, Pillny M, et al. Prothrombin and factor V mutations in women with a history of thrombosis during pregnancy and the puerperium. N Engl J Med 2000;342:374–80.

[9] Samama MM, Rached RA, Horellou MH, Aquilanti S, Mathieux VG, Plu-Bureau G, et al. Pregnancy associated venous thromboembolism (VTE) in combined heterozygous factor V Leiden (FVL) and prothrombin (FII) 20210A mutation and in heterozygous FII single gene mutation alone. Br J Haematol 2003;123:327–34.

[10] Mc Coll MD, Ramsay JE, Tait RC, Walker ID, Mc Call F, Conkie JA, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997;78:1183–8.

[11] Martinelli I, De Stefano V, Taioli E, Paciaroni K, Rossi E, Mannucci PM. Inherited thrombophilia and first venous thromboembolism during pregnancy and puerperium. Thromb Haemost 2002;87:791–5.

[12] Greer IA. Thrombosis in pregnancy : maternal and fetal issues. Lancet 1999;353:1258–65.

[13] Prandoni P, Lensing AW, Prins MH, Bernardi E, Marchiori A, Bagatella P, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 2002;137:955–60.

[14] Janssen HF, Schachner J, Hubbard J, Hartman T. The risk of deep venous thrombosis: a computerized epidemiologic approach. Surgery 1987;101:205–12.

[15] Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. Obstet Gynecol Surv 1999;54: 265–71.