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The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis

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Summary

Whether or not pregnant women with a previous episode of venous thromboembolism (VTE) should receive antithrombotic prophylaxis is a matter of debate. In order to estimate the rate of recurrent deep venous thrombosis (DVT) or pulmonary embolism (PE) during pregnancy and puerperium we retrospectively investigated a cohort of 1104 women with previous VTE; after a single DVT or isolated PE, 88 of them became pregnant at least once without receiving antithrombotic prophylaxis. Overall, 155 pregnancies and 120 puerperium periods without prophylaxis were recorded. There were nine recurrences during pregnancy and 10 during puerperium, with a rate of 5·8% [95% confidence interval (CI) 3·0–10·6] and 8·3% (95%CI 4·5–14·6) respectively. In pregnancy, the rate of recurrence was 7·5% (95%CI 4·0–13·7) if the first VTE was unprovoked, related to pregnancy or to oral contraceptive use, whereas no recurrence occurred if the first VTE was related to other transient risk factors. In puerperium, the rate of recurrence was 15·5% (95%CI 7·7–28·7) in women with a pregnancy-related first VTE, with a risk 3·9-times higher than in the remaining women. Inherited thrombophilia was not associated with a statistically significant increase in risk of recurrence in pregnancy or in puerperium, yet the rate of recurrence in puerperium was 14·2% (95%CI 5·7–31·4) in overall carriers of factor V Leiden and 30% (95%CI 10·7–60·3) in carriers with a pregnancy-related first VTE, with a risk 6·8 times higher than in women without thrombophilia and with a non pregnancy-related first VTE.

Keywords: pregnancy, puerperium, inherited thrombophilia, recurrent venous thromboembolism.

The annual incidence of venous thromboembolism (VTE) among women of childbearing age is 0·18 per 1000 (Nordstrom *et al*, 1992) and this increases to 0·71–1·3 per 1000 when related to pregnancy (McColl *et al*, 1997; Andersen *et al*, 1998; Lindqvist *et al*, 1999). The approximately fourfold increased risk of a first VTE in pregnancy increases up to 14-fold during puerperium (Rosendaal, 1999), and is further increased in carriers of inherited thrombophilia (Martinelli *et al*, 2001, 2002). Although antithrombotic prophylaxis is warranted during puerperium in women who have had a previous VTE, no definite recommendation is given for the antepartum period (Bates *et al*, 2004). Antithrombotic prophylaxis with low-molecular weight heparin during pregnancy has been suggested in women with a first VTE that had occurred in the absence of circumstantial risk factors, during pregnancy or oral contraceptive use and in women with inherited thrombophilia (Bates *et al*, 2004). However, a paucity of data supports this recommendation (Tengborn *et al*, 1989; Brill-Edwards *et al*, 2000; Simioni *et al*, 2001; Pabinger *et al*, 2005). This study aimed to estimate the rate of recurrent VTE during pregnancy and puerperium in women who did not receive antithrombotic prophylaxis, and to assess whether or not inherited thrombophilia and the circumstances of occurrence of the first VTE predicted the risk of recurrent VTE.

Patients and methods

Patients

The initial cohort comprised 1104 women who had had a first VTE before the age of 40 years, and were referred to the Thrombosis Centres in Rome and Milan for thrombophilia

screening between 1995 and 2005. All patients were interviewed about their medical history before physicians were aware of the results of thrombophilia testing. The presence of the following putative risk factors at the time of VTE was recorded: surgery, pregnancy and puerperium, oral contraceptive use, trauma, leg casting, prolonged bed immobilization (>10 d) and air travel, for lower-limb deep vein thrombosis (DVT) and pulmonary embolism (PE); for upper-limb DVT, strenuous muscular effort with the arms and for cerebral and splanchnic venous thrombosis, local infections were also recorded as putative risk factors. In the absence of the aforementioned risk factors, VTE was considered unprovoked. No patient had overt cancer, chronic myeloproliferative disease, autoimmune disorder or liver failure.

All information provided by the patients was validated by careful examination of their medical records; special attention was given to the circumstances of first or recurrent VTE, including the presence of risk factors, the gestational week if the VTE was pregnancy-related and the diagnostic procedures.

Diagnosis of DVT was accepted when objectively confirmed with compression or colour-Doppler ultrasonography or venography, PE diagnosis was by perfusion lung scanning, computed tomography or magnetic resonance imaging, and that of cerebral or abdominal vein thrombosis with computed tomography or magnetic resonance imaging. The objective diagnosis of recurrent VTE was made when it occurred after at least 3 months from the first event in a new venous area or if an extension of the initial thrombus was objectively documented. Episodes of superficial vein thrombosis objectively diagnosed with ultrasonography were also recorded, but they were not computed as recurrences.

At the time of referral to the Thrombosis Centres, all patients gave informed consent for laboratory investigation and underwent thrombophilia screening, including measurement of plasma antithrombin (AT) and protein C (PC) functional activities, free protein S (PS) antigen, DNA analyses for factor V Leiden (FVL) and prothrombin (PT) 20210A polymorphisms, and search for antiphospholipid antibodies (i.e. lupus anticoagulant and anticardiolipin antibodies). The laboratory methods were based on current standard procedures (Martinelli *et al*, 2001, 2002). Measurement of the naturally occurring anticoagulant proteins was carried out in the absence of potentially interfering factors (such as oral contraceptives or hormonal replacement therapy, recent pregnancy, oral anticoagulant therapy), but their deficiencies were considered inherited only if levels below the normal range were also found in at least one first-degree relative.

Statistical methods

Statistical analysis was performed using the software GRAPHPAD PRISM 3·0 (GraphPad Software, Inc., San Diego, CA, USA). Differences between groups were estimated by the Fisher's exact test or by the chi-square test when appropriate (statistical significance for $P < 0{\cdot}05$). The relative risk (RR) with 95% confidence interval (95% CI) was estimated for each subject and calculated by a 2×2 contingency table to estimate the risk of recurrent VTE during pregnancy or puerperium. The cumulative probability of recurrence according to the period of pregnancy was analysed by of the Kaplan–Meier method; in order to ensure the independence of the observations, only the first pregnancy after VTE was considered. Pregnancies without recurrent VTE were censored at the week of delivery, fetal loss or termination.

Results

Identification of the patient cohort

Of the initial cohort of 1104 women, those who did not become pregnant after the first VTE and those with antiphospholipid antibodies were excluded. Of 123 women who became pregnant at least once after the first VTE, 35 were excluded from the study because they had had recurrent VTE (at least two episodes) before being pregnant ($n = 7$) or because they received antithrombotic prophylaxis during all the pregnancies that occurred after their first VTE ($n = 28$). Circumstances associated with the first VTE in these 35 women were oral contraceptive use in seven (20%), pregnancy or puerperium in 15 (42·9%), other transient conditions in seven (20%) and none (unprovoked VTE) in six (17·1%). Fifteen women (42·9%) were diagnosed as carriers of inherited thrombophilia.

Thus, 88 women who had a single episode of VTE and subsequently became pregnant at least once without receiving antithrombotic prophylaxis during pregnancy were the study population. Overall, 155 pregnancies (115 ending in live births) and 120 puerperium periods (defined as 6 weeks after delivery at ≥16 weeks' gestation) were recorded and analysed.

Inherited thrombophilia was found in 35 of the 88 women (39·7%); four had AT, PC, or PS deficiencies, 19 FVL (one homozygote), eight PT20210A and four multiple abnormalities (heterozygosity for FVL combined with AT deficiency in two patients and with heterozygous PT20210A in two). The general characteristics of the study population are shown in Table I.

The prevalence of inherited thrombophilia and of that of the circumstances at first VTE did not significantly differ between the 88 women included in and the 35 women excluded from the study.

Pregnancy-related recurrent VTE in the whole cohort

Nineteen women (21·5%, 95% CI 14·2–31·2) had a pregnancy- or a puerperium-related recurrent VTE, with an overall rate of 12·2% (95% CI 7·9–18·3) among the 155 recorded pregnancies; recurrences were 16 DVTs of the legs, 1 DVT with PE, and 2 PE. Nine recurrences occurred during pregnancy (5·8%, 95% CI 3·0–10·6) and 10 during puerperium (8·3%, 95% CI 4·5–14·6); five pregnancy- and six puerperium-related recurrent VTE occurred during the first pregnancy after the first VTE.

Table I. General characteristics of the study population, type of the first venous thromboembolism (VTE), thrombophilia and circumstantial risk factors.

No. of women	88
Age at first VTE, median (range), years	25·5 (6–40)
Primigravidae after first VTE, *n* (%)	36 (40·9)
No. of pregnancies	155
Live births	115
Fetal loss <16th week	35
Fetal loss ≥16th week	5
Type of first VTE, *n* (%)	
Lower-limb DVT ± PE	78 (88·6)
PE alone	5 (5·7)
Upper-limb DVT	2 (2·3)
Cerebral vein thrombosis	2 (2·3)
Splanchnic vein thrombosis	1 (1·1)
Type of inherited thrombophilia, *n*(%)	
None	53 (60·2)
Factor V Leiden	19 (21·5)
Prothrombin G20210A	8 (9·1)
Antithrombin, protein C or protein S deficiency	4 (4·6)
Multiple abnormalities	4 (4·6)
Circumstantial risk factors at first VTE, *n*(%)	
None	21 (23·9)
Oral contraceptive use	14 (15·9)
Pregnancy	10 (11·4)
Puerperium	23 (26·1)
Other transient risk factors *	20 (22·7)

*Surgery in four, trauma in five, prolonged bed immobilization in nine and air travel in two patients.

The risk of recurrent VTE occurring during puerperium was not significantly higher than during pregnancy (RR 1·4, 95% CI 0·6–3·4). Of the nine antepartum recurrences, four occurred during the first trimester of gestation, two during the second and three during the third ($P = 0·60$ by chi-square test). The cumulative probability of VTE recurrence during the first pregnancy after VTE was 2·4% (95% CI 0·0–5·6) at the 12th week, 4·9% (95% CI 0·2–9·6) at the 24th week, and 6·2% (95% CI 0·9–11·5) at the end of gestation (Fig. 1). Finally, superficial vein thrombosis of the legs occurred in three women (in one case during pregnancy and in two cases during puerperium).

Pregnancy-related recurrent VTE according to the presence of thrombophilia or to the circumstances associated with the first event

The rate of recurrence was similar in carriers and non-carriers of thrombophilia during both gestation ($P = 0·48$) and puerperium ($P = 1·0$) (Table II). The risk of recurrent VTE estimated by patient was not significantly higher in carriers of thrombophilia than in non-carriers (Table III). FVL carriers had a rate of recurrent VTE during the recorded puerperium periods as high as 14·2% (95%CI 5·7–31·4), but the increase in risk estimated by patient was not statistically significant in comparison with women without thrombophilia (Table III).

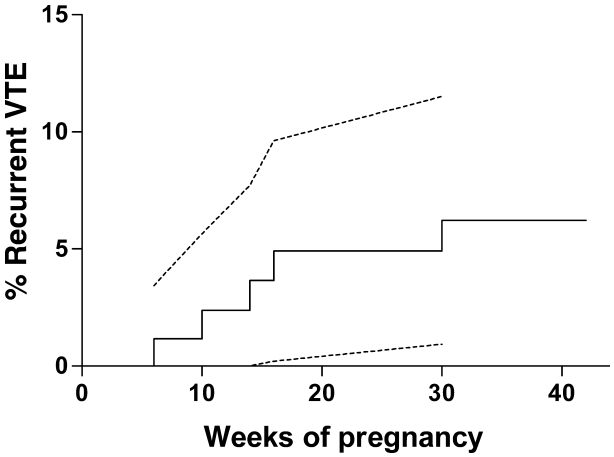

Fig 1. Cumulative probability of recurrent venous thromboembolism (VTE) during the first pregnancy after a first VTE. The broken lines indicate the 95% confidence intervals.

The rate of recurrent VTE during the recorded pregnancies varied between 4·2% and 9·8% among women who had had their first VTE unprovoked, related to pregnancy or oral contraceptive use, with no statistically significant difference between the groups ($P = 0·54$) (Table II). No recurrent VTE during pregnancy was recorded in women with a first VTE that had occurred in the presence of other transient risk factors (Table II). After excluding these women, the rate of recurrent VTE during pregnancy was 7·5% (95% CI 4·0–13·7), with a cumulative probability of recurrence at the end of pregnancy of 8·1% (95% CI 1·3–15·0).

The rate of recurrent VTE during the recorded puerperium periods was 15·5% in women with a pregnancy-related first VTE, 3·1% in women with a first unprovoked VTE, and 7·1% in women with a first VTE that occurred in the presence of transient risk factors; no recurrence during puerperium was recorded in women with a first VTE related to oral contraceptive use (Table II). Overall, women with a pregnancy-related first VTE had a 3·9-fold higher risk (95% CI 1·1–14·0) of recurrence in puerperium, compared with women with a first VTE related to other circumstances (Table III). The contemporary presence of FVL and a first pregnancy-related VTE was associated with a 7·1% (95% CI 1·2–31·4) rate of recurrent VTE in pregnancy and a 30% (95%CI 10·7–60·3) rate in puerperium. In these women the risk of puerperium-related recurrent VTE was 6·8 times higher (95% CI 1·4–33·7) than in non-carriers with a non-pregnancy-related first VTE (Table - III).

Discussion

During pregnancy haemostasis is shifted towards hypercoagulability (Kjellberg *et al*, 1999; Hellgren, 2003), and the risk of recurrent VTE in women who had had a first VTE is likely to be increased in pregnancy in comparison with the periods outside pregnancy (Pabinger *et al*, 2002). When evaluating the

Table II. Rate of recurrent venous thromboembolism (VTE) during the recorded pregnancies and puerperium periods according to the presence or absence of thrombophilia and the circumstances of the first event.

	No. of women	No. of recurrent VTE/no. of pregnancies% (95% CI)	No. of recurrent VTE/no. of postpartum periods% (95%CI)
Thrombophilia			
Yes (all types)	35	5/63 7·9 (3·4–17·2)	4/45 8·8 (3·5–20·7)
Yes (factor V Leiden only)	19	2/39 5·1 (1·4–16·8)	4/28 14·2 (5·7–31·4)
No	53	4/92 4·3 (1·7–10·6)	6/75 8·0 (3·7–16·3)
Risk factors at first VTE			
None	21	2/47 4·2 (1·1–14·2)	1/32 3·1 (0·5–15·7)
Oral contraceptive use	14	2/21 9·5 (2·6–28·9)	0/15
Pregnancy/puerperium	33	5/51 9·8 (4·2–20·9)	7/45 15·5 (7·7–28·7)
Other transient risk factors	20	0/36	2/28 7·1 (1·9–22·6)

Table III. Relative risk (RR), estimated by patient, of recurrent venous thromboembolism (VTE) during pregnancy and puerperium without antithrombotic prophylaxis according to thrombophilia and circumstances of first event.

	Pregnancy		Puerperium	
	Women (VTE), *n*	RR (95% CI)	Women (VTE), *n*	RR (95% CI)
Thrombophilia				
No	53 (4)	Ref.	53 (6)	Ref.
Yes	35 (5)	1·9 (0·5–6·6)	35 (4)	1·0 (0·3–3·3)
Factor V Leiden (FVL)				
No	53 (4)	Ref.	53 (6)	Ref.
Yes*	19 (2)	1·4 (0·3–7·0)	19 (4)	1·9 (0·6–5·9)
First VTE pregnancy-related				
No	55 (4)	Ref.	55 (3)	Ref.
Yes	33 (5)	2·1 (0·6–7·2)	33 (7)	3·9 (1·1–14·0)
FVL + first VTE pregnancy-related				
No*	32 (1)	Ref.	32 (2)	Ref.
Yes	7 (1)	4·6 (0·3–64·6)	7 (3)	6·8 (1·4–33·7)

*No other thrombophilic abnormalities.

administration of antithrombotic prophylaxis during pregnancy in women with previous VTE, the risk of treatment-related complications must be weighed against the risk of developing a pregnancy-related recurrence. Limited data are available on the magnitude of such risk (Tengborn *et al*, 1989; Brill-Edwards *et al*, 2000; Simioni *et al*, 2001; Bates *et al*, 2004; Pabinger *et al*, 2005). The rate of pregnancy-related recurrent VTE in the absence of antithrombotic prophylaxis varied, from 2·4% in a prospective study (Brill-Edwards *et al*, 2000) to 11·1% in a small retrospective study (Tengborn *et al*, 1989), and was 4% in a large retrospective study (Pabinger *et al*, 2005), These studies showed that the risk of pregnancy-related recurrent VTE is higher in women with inherited thrombophilia (Brill-Edwards *et al*, 2000; Pabinger *et al*, 2005), and in those who had had a first unprovoked VTE (Brill-Edwards *et al*, 2000), or that occurred during oral contraceptive use (Pabinger *et al*, 2005). In a small retrospective study carried out in women with inherited thrombophilia, the rate of antepartum recurrent VTE was reported to be as high as 21·4% (Simioni *et al*, 2001). The low rate of pregnancy-related recurrence in the prospective study (Brill-Edwards *et al*, 2000) led to the claim that the haemorrhagic risk associated with the treatment with heparin outweighed the risk of recurrent VTE. However, women with known thrombophilia or recent VTE were excluded, leading to a possible underestimation of the risk of recurrence, and the mean duration of

pregnancy at the time of recruitment was 15 weeks, so that information on the risk of recurrence in the first trimester of pregnancy was lost.

In the present study, the rate of pregnancy-related recurrent VTE was 5·8% in pregnancy and 8·3% in puerperium. The overall rate of pregnancy-related recurrent VTE was approximately 12 per 100 pregnancies, i.e. 120-fold higher than the baseline risk of one pregnancy-related first VTE per 1000 pregnancies. Looking at the conditions that might increase the risk of recurrent VTE during pregnancy (e.g. inherited thrombophilia and the circumstances of first VTE occurrence), we found that the presence of thrombophilia was not associated with an increased risk and that a first unprovoked VTE or those that occurred during pregnancy or oral contraceptive use were associated with an approximately 7% rate of recurrence. In puerperium, the risk of recurrent VTE was 3·9-fold higher in those with a pregnancy-related first VTE. The rate of recurrent VTE in puerperium was 15·5%, 7·1% and 3·1% respectively, in women with a pregnancy- or puerperium-related first VTE, with VTE associated with other circumstantial risk factors, and with unprovoked VTE. In our cohort, 36% of women with a pregnancy-related first VTE had a pregnancy-related recurrence, whereas only 13% of women with other circumstances associated with the first VTE had a pregnancy-related recurrence. It could be hypothesised that such tendency to replicate the same scenario during pregnancy and puerperium might be in part explained by individual anatomical characteristics that favour compression of the pelvic vessels by the gravid uterus or by individual hormonal patterns of pregnancy-related changes that favour hypercoagulability.

The retrospective design of this study does not allow any conclusions to be drawn on antithrombotic prophylaxis during pregnancy, but adds information on the magnitude of the risk of recurrent VTE. The present study did not consider the obstetric history of the patients after their referral to our centres and we carried out a pure retrospective analysis. Therefore, all the decisions regarding the administration of antithrombotic prophylaxis during these pregnancies occurred between VTE and the referral to the thrombosis centres and were taken by the care physicians, who were not influenced by knowledge of the thrombophilia status. The diagnosis of first or recurrent VTE was validated by the investigators at the thrombosis centres, who were blinded to the laboratory results. Finally, as the rate of women subsequently diagnosed as having inherited thrombophilia and the circumstantial risk factors associated with first VTE were similar among women included in and those excluded from the study, it is unlikely that a selection bias could have influenced the risk estimates.

The risk of recurrence after a single VTE is increased during pregnancy, but is absent if the first VTE was related to transient risk factors other than pregnancy, puerperium or oral contraceptive use. Therefore this study suggests that in women with previous VTE the antithrombotic prophylaxis during pregnancy should be tailored according to the circumstances at the first event, considering that women who had suffered a first VTE that was unprovoked, pregnancy-related or oestrogen-related had a higher rate of recurrent VTE. In this setting, puerperium was confirmed to be the period that carried a higher risk of recurrent VTE; in women with FVL or a pregnancy-related first VTE, the rate of puerperium-related recurrent VTE was further increased to 15%, so that antithrombotic postpartum prophylaxis seems particularly warranted in these women. However, due to the small number of recurrent events after stratification according to the circumstances at the first VTE or to the presence of thrombophilia, the data concerning such subgroups should be interpreted with caution and deserves further investigation.

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