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Temporary increase in the risk of recurrence during pregnancy in women with a history of venous thromboembolism

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**TEMPORARY INCREASE IN THE RISK OF RECURRENCE DURING PREGNANCY IN WOMEN
WITH A HISTORY OF VENOUS THROMBOEMBOLISM**

SHORT TITLE: RECURRENT PREGNANCY ASSOCIATED THROMBOSIS

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There is strong evidence that the incidence of venous thromboembolism (VTE) is increased during pregnancy. However, it is not known whether and to which extent pregnancy influences the risk of recurrent VTE in women with previous thrombosis. To investigate, whether pregnancy temporarily increases the risk of recurrent thrombosis, we retrospectively evaluated the recurrence rate in 109 women who had at least one pregnancy after an episode of VTE by comparing the time-period during pregnancy to the non-pregnant period. Forty-three women had a first recurrence during a total observation time of 1014 years. Eight events (73 observation years) occurred during, 35 (941 observation years) outside pregnancy. Recurrence rate per 100 patient-years was 10.9 during and 3.7 outside pregnancy. The relative risk during pregnancy was 3.5 (95% confidence interval 1.6 – 7.8, $p = 0.002$). Our data suggest that pregnancy leads to a temporary increase in the risk of recurrent thrombotic events.

Introduction

Venous thromboembolism is an infrequent but leading cause of maternal mortality¹. There is ongoing debate, whether or not pregnant women with previous venous thrombosis should routinely receive prophylactic anticoagulation. Estimates of the rate of recurrent VTE during pregnancy vary, in retrospective studies data up to 11% have been found². Recently, in a prospective study Brill-Edwards and others³ found a low risk of recurrent antepartum VTE despite withholding prophylactic anticoagulation and concluded that antepartum prophylaxis should be considered only in patients with idiopathic thrombosis and those with thrombophilia.

In the general population pregnancy increases the risk for VTE about 5fold⁴. There are no data in the literature how pregnancy influences the risk of recurrent VTE in women with previous thrombosis. To investigate, whether pregnancy temporarily increases the risk of recurrent thrombosis, we studied women with a history of VTE and evaluated their risk of recurrence during pregnancy in comparison to periods when they were not pregnant.

Study design

Patients

Nine-hundred-and-seventy-three consecutive women with a history of objectively confirmed VTE that had occurred between the age of 13 - 45 years were investigated

for risk factors of thrombosis between 1985 and 1998 and were invited for reinvestigation in 1999. Five-hundred-and-seven women followed our invitation, had a blood sample drawn and underwent a standardized interview on their history of thrombosis and pregnancy associated complications⁵. Hundred-and-nine women had at least one pregnancy (in total 180 pregnancies) without thrombosis prophylaxis after a single VTE and were included into the study. The median age was 38 years (range 22–76 years) at inclusion and 24 years (range 14–42 years) at first VTE. At first thrombosis 94 women had at least one temporary risk factor: 56 had oral contraceptives (OC) , 14 surgery (5 with additional OC), 11 trauma (6 with OC), 5 pregnancy, 15 delivery, 7 immobilization (5 with OC) and 2 had other conditions. Fifteen women had no temporary risk factor at first event. Thrombosis risk factors in the patients were determined as previously described⁵ and are listed in Table 1. Recurrent thrombotic events were categorized as definite, when they were objectively confirmed by ultrasonography, phlebography, ventilation-perfusion lung-scan or computed tomography and as probable, when clinical symptoms were typical and had led to anticoagulation.

Statistical analysis

To compare the risk of recurrent VTE during pregnancy to the risk outside pregnancy we evaluated the incidence of thrombosis at the time periods during pregnancy and when patients were not pregnant. The observation period started after cessation of oral anticoagulant treatment after the first VTE (usually 4-6 months) or, if anticoagulant treatment was stopped earlier, 3 months after the first event and ended at the time of first recurrence. The observation time of patients who did not experience a recurrent VTE was censored at the time of the interview. For calculation of the recurrence rate per patient year, the number of recurrent VTE was related to

the total observation time in years⁶. This was done separately for the total observation time during and outside pregnancies. Cox regression⁷ was used to estimate the relative risk of VTE due to pregnancy. In this analysis a time-dependent prognostic factor was considered, describing the varying states of the patients (pregnant or not pregnant) in the course of the observation time. We allowed for temporary exclusions from the risk set, if patients were temporarily not evaluable for the event of interest. This was the case during pregnancies with thrombosis prophylaxis. Patients were also excluded from the risk set for a time period of 6 weeks after each pregnancy, since during this period the risk of recurrent thrombosis is unpredictably high and thrombosis prophylaxis is recommended.

Results and discussion

Forty-three of the 109 women had a first recurrent event during a total observation period of 1014 years, 73 years during and 941 outside pregnancy. Eight events (5 deep leg, 1 deep arm vein thrombosis and 2 pulmonary embolisms) occurred during pregnancy. All events were objectively documented (definite). Five events occurred during the first, 2 during the second and one during the third trimester. No additional triggering factors, like trauma, surgery or immobilisation were present. Four women had a detectable abnormality (4 were heterozygous for factor V: R506Q, two of these with additional hyperhomocysteinemia), 4 had normal laboratory tests (Table 2). In all women with recurrence during pregnancy a temporary risk factor (oral contraceptives in 7, in 3 with an additional trauma, surgery in one) had been present at first event. Thirty-five women had a recurrent event (25 definite, 10 probable) without being pregnant. Twenty-five recurrent events occurred without a temporary risk factor, 2, while on OC, posttraumatic or during immobilization, respectively, and 4 after surgery. Recurrence rate per patient-year was 10.9% during pregnancy and 3.7% in

the non-pregnant period. Using Cox regression analysis the estimated relative risk during pregnancy was 3.5 (95% confidence interval (CI) 1.6 – 7.8, $p = 0.002$).

The main question is, whether women with previous thrombosis should receive prophylaxis not only after delivery, but also during pregnancy. The low risk of pregnancy associated recurrent VTE in the recently published prospective study³ prompted the authors of the Sixth ACCP Consensus Conference on Antithrombotic Therapy¹ to recommend two general approaches: (1) active prophylaxis with heparin or (2) clinical surveillance and investigation if symptoms suspicious of deep vein thrombosis or PE during pregnancy occur without routinely giving prophylactic anticoagulation. In the prospective study published by Brill-Edwards et al³ the recurrence rate was low (3 events during 125 pregnancies), a comparison to periods outside pregnancy was not performed. Although the study had a prospective design, there are several limitations. The enrollment of the vast majority of patients was after the first trimester, the mean duration of pregnancy at enrollment was 15 ± 6 weeks. It might be suggested that thromboembolic events occurring during the first and the second trimester were missed. Furthermore, no information on the duration and outcome of pregnancy is provided. Data on abortion, stillbirth or premature delivery and a therefore shortened period at risk are not given. Thus, it might be that in this prospective study the recurrence rate is underestimated. Our retrospective study covered the whole period of pregnancy and takes also into consideration pregnancies that ended prematurely. Therefore an exact estimate on the recurrence/patient year could be performed.

Our data suggest that pregnancy leads to a temporary and more than three-fold increase in the risk of symptomatic recurrent thrombosis. Temporary risk factors at first event or the investigation for thrombosis risk factors seem not to differentiate clearly between women at high or low risk for pregnancy associated recurrence. Most probably prophylactic heparin can reduce the incidence of thrombosis during pregnancy. Possible disadvantages of prophylactic heparin during pregnancy are inconvenience for the woman, costs and, although infrequent, bleeding, osteoporosis or heparin induced thrombocytopenia. However, from a systematic review of 486 pregnancies⁸ LMWH can be regarded as safe. During the 486 pregnancies there was no clinically important bleeding or heparin induced thrombocytopenia, one case of symptomatic osteoporosis and only 3 cases of VTE were reported.

Since the study is retrospective, it has certain limitations. Thromboembolic events were objectively confirmed in each pregnancy associated episode, however, part of the events outside pregnancy were not confirmed. By not including these events, the relative risk during pregnancy

would even be higher. Furthermore our overall recurrence rate is not high in comparison to the results from most published studies on recurrence rates^{9,10,11} and was close to that observed in the prospective AUREC study in individuals without elevated factor VIII levels, where a likelihood of recurrence at two years of 5% was observed¹².

During pregnancy the recurrence rate was significantly higher (10.9 per 100 patient years). Recurrent VTE is a serious complication of pregnancy, since it is potentially life threatening and a recurrent thrombotic event increases the probability for a postthrombotic syndrome⁹. The time of pregnancy and the postpartum period delineate a well defined period of increased risk. Prophylactic administration of LMWH during pregnancy might reduce the risk for this pregnancy-associated thrombosis and thus the overall recurrence rate in this young patient population and probably does not have the disadvantage of a high bleeding risk that is observed during oral anticoagulant treatment¹³. However, it remains to be shown in well designed randomized trials that prophylactic anticoagulation is definitely able to decrease the rate for pregnancy associated recurrent VTE and to establish its safety.

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Table 1: Laboratory Risk Factors for Thrombosis in 109 Women With a History of VTE

Risk Factors	Patients with Abnormality/Total	Percentage
None	39/101*	39
Heterozygous factor V: R506Q	38/109	35
Homozygous factor V: R506Q	5/109	4.6
Heterozygous G20210A prothrombin	8/107	7.5
Antithrombin deficiency	2/109	1.8
Protein C deficiency	5/109	4.6
Protein S deficiency	5/109	4.6
Hyperhomocysteinemia	11/101	11
Elevated factor VIII	12/102	12
Lupus anticoagulant	3/109	2.8
Of these		
Two risk factors combined	13/101*	13
Three risk factors combined	3/101*	3

*In 101 women all risk factors were determined

Table 2: Recurrent VTE during Pregnancy and Risk Factors at First Event in 109 Women with a History of VTE

Temporary risk factor	no	yes	no	yes
Laboratory risk factor	yes	yes	no	no
Women (n)	9	55	6	39
Recurrence (n)	0	4	0	4
Recurrence rate (%)	0	7.3	0	10.3

Temporary risk factors: OC use, pregnancy, surgery, trauma, immobilisation

Laboratory risk factors: Antithrombin-, protein C- or S-deficiency, factor V:R506Q, G20210A prothrombin gene variation, hyperhomocysteinemia, elevated factor VIII, lupus anticoagulant