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Factor V Leiden mutation and the risk of venous thromboembolism in pregnant women

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Background and Objectives. In this retrospective, single center, cohort study we assessed the risk of pregnancy-related venous thromboembolism (VTE) in women belonging to a large number of families identified because of a symptomatic proband with single identified factor V Leiden mutation.

Design and Methods. Female family members who had experienced at least one full-term pregnancy were enrolled in the study. Two hundred and seventy pregnancies occurred in 105 carriers and 215 pregnancies in 81 non-carriers of factor V Leiden mutation.

Results. The frequency of VTE was 6.4% for heterozygous, 16.7% for homozygous, 20% for double heterozygous carriers of thrombophilic defects, and 1.2% for non–carriers. The majority of VTE events related to pregnancy occurred in the post-partum period. The relative risks of developing pregnancy-related VTE in women who were carriers of heterozygous and homozygous (or combined heterozygous) factor V Leiden mutation as compared to non-carriers were 5.3 (95% CI, 0.6 to 43.9) and 15.4 (95% CI, 1.4 to 164), respectively.

Interpretation and Conclusions. Factor V Leiden mutation is a risk factor for pregnancy-related VTE, especially in its homozygous form and in combination with other thrombophilic abnormalities. Screening of families with this mutation might be useful for women of fertile age, as they may take advantage from thromboprophylaxis during pregnancy and the post-partum period.

Key words: factor V Leiden, homozygous defect, pregnancy, venous thromboembolism.

Pregnancy, puerperium and oral contraceptive treatment are potential risk factors for venous thromboembolism (VTE) in women of fertile age.[1,2] The incidence of VTE in women during pregnancy is around 1 per 1,000[3,4] and increases ten times during the post-partum period.[5] These estimates are considerably higher than those reported for women of similar age in the general population.[6] Many thrombotic events occurring during pregnancy or the post-partum period develop in women with underlying thrombophilia. Women with heterozygous deficiency of antithrombin, protein C or protein S have a definitely higher risk of pregnancy-related thrombosis than non-deficient women.[7] Accordingly, thromboprophylactic drugs are generally administered during pregnancy and puerperium to women with these deficiencies. These clotting inhibitor deficiencies, however, are relatively rare. In contrast, other genetic defects predisposing to thrombosis such as factor V Leiden mutation and prothrombin variant G20210A are quite common in the general population. Factor V Leiden mutation is present in as many as 5% of the general Southern European population and the prevalence rises to 16-50% in patients with VTE. It has been shown that factor V Leiden is a mild thrombophilic defect that confers a moderately increased risk of VTE in carriers as compared to in non-carriers.[8] Pregnancy, puerperium and oral contraceptive treatment may increase the thrombotic risk in carriers of factor V Leiden mutation.[9-13]

We evaluated the incidence of pregnancy-related VTE in women selected because of family screenings for factor V Leiden mutation, and assessed the relative risk of VTE in carriers as compared to in non-carriers. This information is important for decision making concerning the administration of thromboprophylaxis during pregnancy and puerperium.

Design and Methods

Patients

Patients with a single identified factor V Leiden mutation and an objective diagnosis of venous thromboembolism were recruited in our Thrombosis Center from May 1994 to June 2000. Family members of probands with combined thrombophilic defects (either clotting inhibitor deficiencies or prothrombin variant combined with factor V Leiden mutation) were not included in this study. Their first and second-degree female relatives who had been pregnant at least once were eligible for the study. Women older than 15 years who were heterozygous carriers of factor V Leiden mutation were compared to women from the same families without the defect. A detailed medical history was obtained from all women by a physician unaware of the deficiency status of the patient. Particular attention was paid to thromboembolic events which had occurred and risk-periods experienced. The diagnosis of VTE had to be objectively documented. This objective documentation was defined as deep vein thrombosis confirmed by compression ultrasonography, impedance plethysmography, or Doppler-ultrasound. In the absence of objective tests at the time of thrombosis, the diagnosis was accepted if anticoagulant treatment had been administered for at least three months after the event. Venous thromboembolism was considered pregnancy-related if it had occurred during pregnancy or in the post-partum period (within three months after childbirth).

In women with a positive past history of VTE, subsequent pregnancies were not considered.

Laboratory analysis

DNA analysis for factor V Leiden mutation was performed as previously described.[14] All women were also tested for the presence of antithrombin, protein S, protein C, hyperhomocysteinemia, lupus anticoagulant and prothrombin variant G20210A according to methods previously described.[7,15-17]

Statistical analysis

In each group the frequency of pregnancy-related VTE was calculated by dividing the number of thrombotic episodes by the total number of pregnancies in each group of women. The relative risk (RR) (and its 95% CI) of pregnancy-related VTE was calculated by dividing the incidence rate in carriers by the incidence rate in non-carrier family members. The relative risk was considered to be statistically significant when the lower limit of the 95% CI was > 1.0.

Results

Out of 407 female family-members belonging to 95 selected families, 186 women had had at least one pregnancy and formed the study population. Of these, 105 were carriers of factor V Leiden mutation (6 homozygous, 94 heterozygous, 2 double heterozygous for factor V Leiden and HR2 haplotype, and 3 double heterozygous for factor V Leiden and prothrombin variant G20210A) and 81 had normal coagulation. The two groups were matched for age, number of pregnancies and age at pregnancies.

The 105 carriers had 270 pregnancies. The 81 non-carriers had 215 pregnancies. Table 1 shows the frequency of VTE events during pregnancy/post-partum according to the deficiency status to be 16.7%, 20% and 6.4% in homozygous, double heterozygous and

Table 1. Risks of pregnancy/post-partum-related VTE in the female family members investigated.

	Number of pregnancy post -partum periods	*Number of VTE events*	*Absolute risk per pregnancy post-partum periods (95% CI)*	*Absolute risk per women during pregnancy post-partum (95% CI)*
Non-carriers (n =81)	215	1(pp)	0.46 % (0.012 to 2.6)	1.2 % (0.03 to 6.9)
Carriers of heterozygous F.V Leiden alone (n =94)	242	6 (4pp)	2.48% (0.9 to 5.4)	6.4% (2.3 to 13.9)
Carriers of double heterozygous defect (n =5)	14	1(pp)	7.1% (0.18 to 39.8)	20% (0.5 to 111)
Carriers of homozygous F.V Leiden (n =6)	14	1	7.1% (0.18 to 39.8)	16.7% (0.4 to 92.9)

Table 2. Main characteristics of the nine women with pregnancy-related VTE.

Patients No.	*Type of defect*	*Age at the time of VTE (years)*	*Site of VTE*	*Period of pregnancy*	*N°. of previous uncomplicated pregnancies*
1	Heterozygous F.V Leiden	40	Right femoro-popliteal DVT	1 month post-partum	1
2	Heterozygous F.V Leiden	29	Left femoro-popliteal DVT	Third trimester	1
3	Heterozygous F.V Leiden	23	Right popliteal DVT	10 days post-partum	0
4	Heterozygous F.V Leiden	34	Left popliteal DVT	20 days post-partum	1
5	Heterozygous F.V Leiden	24	Right popliteal DVT	First trimester	0
6	Heterozygous F.V Leiden and heterozygous F.V HR2 haplotype	31	Right popliteal DVT	10 days post-partum	1
7	Heterozygous F.V Leiden	35	Left femoro-popliteal DVT	15 days post-partum	0
8	Homozygous F.V Leiden	30	Left ilio-femoral DVT	First trimester	1
9	Heterozygous F.V defect (type I) and heterozygous F.V HR2 haplotype (pseudo-homozygous HR2)	40	Left femoro-popliteal DVT and pulmonary embolism	20 days post-partum	5

heterozygous carriers, respectively, and 1.2% of non-carriers. The relative risk for VTE during pregnancy/post-partum in heterozygous women was 5.3 (95% CI, 0.6-43.9) as compared to the risk in non-carriers. Homozygous and double heterozygous carriers taken together had a relative risk of 15.4 (95% CI, 1.4 to 164) as compared to the risk in non-carriers.

The main characteristics of the 9 women who experienced a pregnancy-related VTE are shown in Table 2. It can be observed that the majority of events (5 out of 8 VTE) occurred during the post-partum period in the group of factor V Leiden carriers. Only one VTE occurred in a non-carrier during the post-partum period. Extensive coagulation screening in this patient showed the presence of *pseudo-homozygous* HR2 haplotype (double heterozygous factor V deficiency and HR2 haplotype).[18]

Discussion

The results of our family-study suggest that factor V Leiden is a risk factor for venous thromboembolism during pregnancy and puerperium, at least in its homozygous variant and when combined with other thrombophilic abnormalities. In fact, we found a five-fold (albeit non-significant) higher risk of pregnancy-related VTE in women with heterozygous factor V Leiden mutation than in non-carriers, which is in agreement with the results of previous case-control studies.[11-13] Previous family studies[19,20] have shown an incidence of approximately 2% of pregnancy-related VTE in heterozygous factor V Leiden carriers. Selection criteria of probands in this study, however, were different from those previously used.[20] In fact, probands with combined defects (the majority being represented by combined prothrombin variant and factor V Leiden) were excluded from our study and so, therefore, were their family members. This was not the case in other previously reported family studies, since prothrombin variant 20210A had not been recognized at the time they were started. Carriers of homozygous or double heterozygous defects appeared to have a significantly higher risk of pregnancy-related thrombosis than did non-carriers. Although in our study only a limited number of homozygous or double heterozygous women were included, the risk found has the same order of magnitude as that reported in other studies with similar or different design.[21-26] Unfortunately no prospective evaluation of such a risk is presently available. Interestingly, more than 60% of thrombotic events occurred in the post-partum period, suggesting the need for thromboprophylaxis at least during this period of child-bearing.

Due to our design the study population was made up of women who were relatives of probands with isolated factor V Leiden mutation. As cases and controls differed only for their thrombophilic status, the relative risk for VTE that was found is very likely to reflect the true effect of the mutation during pregnancy. Despite the retrospective design of

our study, the criteria used for VTE diagnosis were strictly defined *a priori*. The medical history was taken by physicians unaware of the patients' factor V Leiden status. In addition, probands were excluded to avoid referral bias.

What are the implications of this study? In agreement with our findings, screening women of fertile age who are family members of symptomatic carriers of isolated factor V Leiden mutation has the potential to identify those at a higher risk of thrombosis during pregnancy and puerperium who might benefit from thromboprophylaxis especially in the post-partum period.[27] In addition, since thrombophilia appears to increase the risk of recurrences in pregnant women with a previous history of VTE,[28,29] family screening also has the potential to detect those women who may require anticoagulant administration rather than simple clinical surveillance during pregnancy. These conclusions cannot be extended to pregnant women outside the context of thrombophilic families, as systematic screening for factor V Leiden as well as prothrombin variant G20210A is probably not cost-effective.[30]

In conclusion, screening for factor V Leiden mutation may be useful for females of fertile age who are family members of probands with a history of VTE. Further clinical trials are required to assess the value of thromboprophylaxis strategies in pregnant women with this mutation, at least in those who are homozygous or carry other thrombophilic abnormalities.

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DT, PS, PP, AG: analysis and interpretation of data; DT, PS, PP, SL, PZ, DS, FF, AG: drafting the article; DT, PS, PP; revising the article critically; DT, PS, PP, SL, PZ, DS, FF, AG: final approval of the version to be submitted.

Disclosures

Conflict of interest: none.

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Manuscript processing

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Potential implications for clinical practice

These data might be helpful in the daily management of thrombophilic families when decisions have to be made on thromboprophylaxis to be given during pregnancy in female family members who are carriers of factor V Leiden mutation. Since this study suggests a different risk of pregnancy-related VTE in heterozygous as compared to homozygous or double heterozygous carriers, it is likely that a different clinical approach to VTE prevention should be considered according to the severity of the thrombophilic defect.

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