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Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis

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Summary. Hormone replacement therapy (HRT) increases the risk of venous thrombosis. We investigated whether this risk is affected by carriership of hereditary prothrombotic abnormalities. Therefore, we determined the two most common prothrombotic mutations, factor V Leiden and prothrombin 20210A in women who participated in a case-control study on venous thrombosis. Relative risks were expressed as odds ratios (OR) with 95% confidence intervals (CI95). Among 77 women aged 45–64 years with a first venous thrombosis, 51% were receiving HRT at the time of thrombosis, compared with 24% of control women (OR = 3.3, CI95 1.8–5.8). Among the patients, 23% had a

prothrombotic defect, versus 7% among the control women (OR = 3.8, CI95 1.7–8.5). Women who had factor V Leiden and used HRT had a 15-fold increased risk (OR = 15.5, CI95 3.1–77), which exceeded the expected joint odds ratio of 6.1 (under an additive model). We conclude that the thrombotic risk of HRT may particularly affect women with prothrombotic mutations. Efforts to avoid HRT in women with increased risk of thrombosis are advisable.

Keywords: venous thrombosis, oestrogens, hormone replacement therapy, factor V Leiden, prothrombin 20210A

Several recent studies have demonstrated that the use of hormone replacement therapy (HRT) is associated with an increased risk of venous thrombosis, i.e. deep-vein thrombosis and pulmonary embolism (Daly *et al.*, 1996; Grodstein *et al.*, 1996; Jick *et al.*, 1996; Grady *et al.*, 2000). The reports pointed to a two- to fourfold increased risk, which is not very different from the relative risk conferred by oral contraceptives (Vessey & Doll, 1968; Stadel, 1981). This was surprising given the low oestrogen and progestogen doses in HRT. As the risk of thrombosis, in absolute terms, is highly dependent on age, these data imply that HRT might lead to a considerable number of excess cases of deep-vein thrombosis among post-menopausal women.

To prevent thrombosis as a result of the use of HRT, it is necessary to identify women at increased risk. Previously, we have demonstrated a synergistic effect between the use of oral contraceptives and the most common prothrombotic

defect, factor V Leiden (Vandenbroucke *et al.*, 1994). Therefore, we hypothesized that women with hereditary thrombophilia would be at high risk of thrombosis when using HRT.

We reinvestigated participants in the Oxford hospital-based case-control study (Daly *et al.*, 1996) of HRT and the occurrence of venous thrombosis for the presence of prothrombotic mutations, which we limited to the two most prevalent abnormalities, factor V Leiden and prothrombin 20210A, each of which is found in several per cent of the general Caucasian population (Rees *et al.*, 1995; Rosendaal *et al.*, 1998). We have reported previously on prothrombotic phenotypes in this group (Lowe *et al.*, 2000).

PATIENTS AND METHODS

The original case-control study included 103 women aged 45–64 years admitted to hospital between April 1990 and December 1994 in the Oxford Regional Health Authority area, with a main diagnosis of a first episode of deep-vein thrombosis or pulmonary embolism (Daly *et al.*, 1996). For comparison, control women were recruited from women

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admitted to hospital for diagnoses unrelated to thrombosis and HRT. Up to two control women were chosen per case, matched by 5-year age group, district of admission and date of hospitalization. Women with a history of stroke, myocardial infarction, malignancies or who had been pregnant, had undergone surgery or had been immobilized in the 6 weeks before admission were excluded from the case and control groups. Results have been published previously (Daly *et al*, 1996).

For the follow-up study in 1995–96 (Lowe *et al*, 2000), all surviving women were invited to take part in a study of thrombotic phenotypes and genotypes. The study was approved by local research ethics committees. Venous blood was obtained from the antecubital vein and anticoagulated with EDTA. DNA was extracted by salting out procedures. DNA analysis for factor V Leiden (factor V G1691A) and prothrombin mutation (G20210A) were performed by standard polymerase chain reaction (PCR) procedures.

We calculated the relative risk associated with HRT and with carriage of a prothrombotic mutation by exposure odds ratios. These indicate the risk of thrombosis in those with the risk factor relative to those without the risk factor. Ninety-five per cent confidence intervals (CI95) were estimated according to the method of Woolf (1955) or derived from the logistic regression model. When numbers were small, exact confidence intervals were computed (Mehta, 1994) using EPI INFO 6 [Centers for Disease Control (CDC), Atlanta, GA, USA]. The original matching is accounted for in our analyses by adjustment for age and district of admission. In some analyses, we grouped factor V Leiden and prothrombin 20210A carriers together. Where numbers allowed, we presented separate risk estimates for both genetic variants. The effect of the combination of prothrombotic mutations was investigated by comparing those with either risk factor and those with both risk factors with those with neither.

RESULTS

DNA was obtained from 77 of the 80 eligible consenting women with venous thrombosis and 163 of the 171 eligible consenting control women. Their general characteristics are shown in Table I.

Among the patients, 51% used HRT at the time of the thrombosis, compared with 24% of control women, which indicated a more than threefold increased risk (OR = 3.3, CI95 1.8–5.8). A prothrombotic mutation (factor V Leiden or prothrombin 20210A) was present in 23% of women with thrombosis (all heterozygous) versus 7% among controls (all heterozygous), with a nearly fourfold increased risk (OR = 3.8, CI95 1.7–8.5). Adjustment for the stratification factors, age and area of admission, did not affect these risk estimates. Factor V Leiden was associated with a fourfold increased risk (OR = 4.0, CI95 1.6–10.2) and prothrombin 20210A with a twofold increased risk (OR = 2.2, CI95 0.2–30.3). Of 18 thrombosis cases with a prothrombotic mutation, eight were hormone users at the time of thrombosis. Of these eight

Table I. General characteristics.

	Patients (n = 77)	Controls (n = 163)
Mean age, years (range)	54 (45–64)	54 (45–64)
Oral anticoagulant therapy (%)	11* (14)	0 (0)
HRT		
At thrombosis† (%)	39 (51)	39 (24)
At venepuncture (%)	18 (23)	52 (32)
Factor V Leiden		
GG (%)	61 (79)	153 (94)
AG (%)	16 (21)	10 (6)
Prothrombin 20210		
GG (%)	75 (97)	161 (99)
AG (%)	2 (3)	2 (1)

*These patients were excluded from previous analyses of haemostatic factors (Lowe *et al*, 2000).

†Or at a similar index date for the controls.

Table II. Factor V Leiden and HRT.

Factor V Leiden	HRT	Patients	Controls	OR	CI95
–	–	30	116	1	
+	–	8	8	3.9	1.3–11.2
–	+	31	37	3.2	1.7–6.0
+	+	8	2	15.5	3.1–76.7

women, five (62%) were in their first year of hormone use, compared with 32% of all cases using HRT (and 23% of controls) (Daly *et al*, 1996).

Subsequently, we investigated the joint effect of prothrombotic mutations and HRT on the risk of venous thrombosis. Whereas HRT and prothrombotic mutations separately each increased thrombotic risk about fourfold, the combination led to an 11-fold increased risk (OR = 11, CI95 2.7–44), which exceeded the expected odds ratio of 7.1 if the risks had been additive. Only four women carried the prothrombin variant, none of whom also used HRT. Given this low number of carriers, separate risk estimates for this variant were not meaningful. Table II shows the separate and joint effects of factor V Leiden and HRT. The combination of factor V Leiden and hormone treatment increased the risk of thrombosis 15-fold (OR = 15.5, CI95 3.1–76.7), clearly exceeding the sum of the separate effects of the two risk factors (expected joint odds ratio 6.1).

DISCUSSION

This reinvestigation of participants in a case-control study of idiopathic venous thrombosis demonstrated that HRT and prothrombotic mutations (factor V Leiden, prothrombin 20210A) increase the risk of venous thrombosis in women aged 45–64 years.

The highest risk of thrombosis was found in women who used HRT and carried the factor V Leiden mutation (15-fold). The increased risk of venous thrombosis in HRT users who are carriers of the factor V Leiden mutation is consistent with our recent report of an increased risk in HRT users with activated protein C (APC) resistance, the thrombotic phenotype associated with this mutation (Lowe *et al.*, 2000). A high thrombotic risk for the combination of hormone use and factor V Leiden was analogous to the synergistic effect we reported previously for oral contraceptive use and factor V Leiden (Vandenbroucke *et al.*, 1994). Furthermore, the new data suggest that the association of the APC-resistant phenotype with increased risk of venous thrombosis, as reported previously (Lowe *et al.*, 2000), results from the pre-existing genetic mutation and not from acquired APC resistance attributable to HRT or venous thrombosis. A second analogy with thrombosis resulting from oral contraceptive use was the association with recent use (Bloemenkamp *et al.*, 2000) for oral contraceptives, we reported a higher risk during the first year of use than for prolonged use, which was most pronounced for women with inherited coagulation defects (Bloemenkamp *et al.*, 2000). In the original case-control study, the risk was increased 3.1-fold during the first year of hormone replacement and 2.1-fold during subsequent years (both relative to non-users) (Daly *et al.*, 1996). The preponderance of first-year users among cases with a prothrombotic mutation (63%) also suggests a higher risk for these women during the first year of HRT use, although the number of women was too small to reach definite conclusions.

The 15-fold increased risk of the combination of HRT and factor V Leiden exceeds the expected joint risk based on the separate effects, which would be a sixfold increased risk (under an additive model). Because of the limited number of women in the group with both risk factors, however, the confidence interval around this estimate was wide.

These results raise a safety issue, in particular the question of how to minimize the use of HRT among women with a high risk of thrombosis. This question is of considerable importance, in particular because recently the long-term arterial benefits of HRT have become doubtful, with randomized trials failing to demonstrate a benefit (Hulley *et al.*, 1998). In making a decision to prescribe HRT, risk minimization strategies may be considered that include detailed history taking (personal and family history of thrombosis) or screening for prothrombotic mutations. Such policies might assist women and clinicians to make rational and informed decisions. Even though a case-control study only allows the calculation of relative risks, and not of absolute risks, we can make some estimates about the effect of selective prescription. The overall incidence of venous thrombosis is one or two per 1000 per year and has a steep age gradient (Rosendaal, 1997). Therefore, in absolute terms, a relative risk of 4 associated with HRT has a much larger impact on women's health than the same relative risk for oral contraceptives, as in women of reproductive age, the incidence is about one per 10000, whereas in

post-menopausal women, it is over one per 1000 per year and increases with more advanced age (Anderson *et al.*, 1991, Nordstrom *et al.*, 1992, Kniffin *et al.*, 1994, Silverstein *et al.*, 1998, Lowe *et al.*, 2000, Oger, 2000).

With a baseline incidence of one to four per 1000 per year in women aged 45–79 years, screening for factor V Leiden with a prevalence of 5%, and subsequent withholding of HRT in those tested positive, would prevent 5–25 thrombotic events annually per 10 000 women screened. With 5 or 10 years of use, screening could well be worthwhile. The effects of screening in preventing thrombosis are likely to be highest in older women. On the other hand, it may prevent more thrombotic events and be more cost-effective to withhold HRT in women with other risk factors for venous thrombosis (such as gross obesity), or in women with a family history of venous thrombosis.

In conclusion, the thrombotic risk of HRT may particularly affect women with prothrombotic mutations, specifically factor V Leiden. Given the high prevalence of this mutation, efforts to minimize prescription of HRT to women with an increased risk should be undertaken. The results presented here are based on a relatively small study and urgently need to be confirmed in a larger study, such as the on-going trials of HRT.

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