Hormone replacement therapy and risk of venous thromboembolism: population based case-control study

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Abstract

Objective: To evaluate the association between use of hormone replacement therapy and the risk of idiopathic venous thromboembolism.

Design: Population based case-control study.

Setting: Population enrolled in the General Practice Research Database, United Kingdom.

Subjects: A cohort of 347 253 women aged 50 to 79 without major risk factors for venous thromboembolism was identified. Cases were 292 women admitted to hospital for a first episode of pulmonary embolism or deep venous thrombosis; 10 000 controls were randomly selected from the source cohort.

Main outcome measures: Adjusted relative risks estimated from unconditional logistic regression.

Results: The adjusted odds ratio of venous thromboembolism for current use of hormone replacement therapy compared with non-users was 2.1 (95% confidence interval 1.4 to 3.2). This increased risk was restricted to first year users, with odds ratios of 4.6 (2.5 to 8.4) during the first six months and 3.0 (1.4 to 6.5) 6-12 months after starting treatment. No major risk differences were observed between users of low and high doses of oestrogens, unopposed and opposed treatment, and oral and transdermal preparations. The risk of idiopathic venous thromboembolism among non-users of replacement therapy was estimated to be 1.3 per 10 000 women per year. Among current users, idiopathic venous thromboembolism occurs at two to three times the rate in non-users, resulting in one to two additional cases per 10 000 women per year.

Conclusions: Current use of hormone replacement therapy was associated with a higher risk of venous thromboembolism, although the risk seemed to be restricted to the first year of use.

Introduction

The deleterious effect of contraceptive oestrogens on the occurrence of venous thromboembolism has sometimes been extrapolated to the use of postmenopausal replacement oestrogens, with the support of scarce data. Early epidemiological studies failed to show an increased risk of venous thromboembolism among users of hormone replacement therapy.¹⁻⁵ However, methodological limitations, including small

sample size and lack of adequate control of confounding, did not allow a lack of association to be established. Some of these limitations have been addressed in three recent observational studies, which consistently showed that the risk of venous thromboembolism among current users of hormone replacement therapy is 2-3.5 times higher than among women not using postmenopausal oestrogens.⁶⁻⁸

To further assess the association between hormone replacement therapy and the risk of venous thromboembolism, we conducted a case-control study nested in a large cohort of women without previous history or other major risk factors for thromboembolism. The cohort was identified through the General Practice Research Database (formerly VAMP) in the United Kingdom. The large size of this cohort allowed for further information on specific aspects of hormone replacement therapy such as the effect of duration of use, oestrogen doses, type of regimen, and route of administration.

Methods

Data source

Data for this nested case-control study were obtained from the information included in the General Practice Research Database in United Kingdom. This is a research oriented database used by general practitioners to register healthcare and medical information about their patients; it covers a general population exceeding 3 million. The information is recorded by general practitioners in a standardised fashion and includes demographic data, all medical diagnoses, consultant and hospital referrals, and a record of all prescriptions issued. Practitioners write the prescriptions directly from the computer, thus ensuring automatic recording. Medication codes are based on the Prescription Pricing Authority's list and a modification of the Oxford Medical Information System (OXMIS) code is used to record diagnoses. Several validation studies have shown that more than 90% of information from the manual medical records of the general practitioners, and more than 95% of newly prescribed drugs, are recorded in the database.^{9 10}

Study population

A cohort of 416 914 women, 50 to 79 years old, registered in the General Practice Research Database between 1 January 1991 and 31 October 1994 was

identified. Those women with a history of venous thromboembolic events or with other risk factors for thromboembolism before 1 January 1991 were identified through the diagnostic information recorded in the database and excluded from the source population. Risk factors were neoplasms, cerebrovascular disease, ischaemic heart disease, heart failure, coagulopathies, vasculitis, and alcohol related diagnoses. The resulting study cohort consisted of 347 253 women who were followed until the first occurrence of one of the five endpoints: code related to venous thromboembolism; risk factor for venous thromboembolism (as above); reaching 80 years of age; death; or end of the study period (31 October 1994).

Detection and ascertainment of cases

Cases were identified through an automated computer search using specific and non-specific OXMIS codes for pulmonary embolism and infarction; deep venous thrombosis and thrombophlebitis; and other venous thrombosis. In this initial step, 674 patients were identified; their computerised information was manually reviewed to ascertain their case status. We considered as a case of idiopathic venous thromboembolism any women admitted to hospital with a first episode of pulmonary embolism or deep venous thrombosis and free of the following risk factors: history of venous thromboembolism, neoplasms, cerebrovascular disease, cardiac disease, coagulopathies, vasculitis, alcohol related diagnoses, and recent fracture, injury, surgery, or hospital admission. Women who had venous thromboembolism while in hospital were not considered cases. The computerised information did not include data on prescribed drugs. After the review, 293 admissions for a first episode of idiopathic venous thromboembolism were confirmed. The remaining 381 patients were dismissed because the diagnosis of pulmonary embolism or deep venous thrombosis was not established or an exclusion criterion was identified (table 1).

To validate confirmed cases, the general practitioners' medical records of a 10% random sample of cases of pulmonary embolism and of deep venous thrombosis were reviewed. Medical records contained information on hospital discharge diagnoses, clinical symptoms, and diagnostic procedures. All cases of pulmonary embolism were confirmed and only one case of deep venous thrombosis was excluded because a

final diagnosis of superficial thrombophlebitis was made. Since the validation process led to high positive predictive values, validation of the rest of identified cases was not performed. In addition, 236 (81%) of the cases had a recorded code for anticoagulant treatment after the episode of thromboembolism. Therefore, 292 cases of idiopathic venous thromboembolism, 97 cases with pulmonary embolism, and 195 cases with deep venous thrombosis were finally included in the analysis. The date of onset of symptoms, when available, or the date of hospital admission was used as the index date.

Selection of controls

A random date within the study period was generated for each of the 347 253 women of the study cohort. All women with a random date included in their period of observation (from study entry to end of follow up) were eligible as controls. This procedure takes into account the amount of time contributed by each woman.¹¹ The same computer based exclusion criteria as those for the cases were applied to all eligible controls, using each woman's random date as her index date. Finally, 10 000 controls were randomly sampled.

Assessment of exposure

A list of all drugs containing oestrogens or progestogens recommended for postmenopausal replacement therapy and available in the United Kingdom during the study period was extracted from the British National Formulary. Replacement drugs were grouped in four regimens: oral conjugated equine oestrogens; transdermal oestradiol; oestradiol implant; and other oral replacement hormones. In addition, each of these regimens was classified as opposed or unopposed depending on whether a progestogen was supplied along with oestrogen. Tibolone was considered as opposed treatment.

For each woman the date of the last prescription for each of the regimens issued before the index date was identified. Three exposure categories for hormone replacement therapy were defined: non-use—women who never had a prescription for hormone replacement therapy recorded in the database; current use—women treated at any time in the six months before the index date; and past use—women who stopped treatment more than six months before the index date. Duration of use of hormone replacement therapy was defined as the period corresponding to consecutive prescriptions, with a maximum interval of 240 days between two prescriptions. The daily dose of oestrogens for each regimen was obtained from the last prescription with dosage instructions among current users.

Statistical analysis

The risk of venous thromboembolism was examined for five exposures to hormone replacement therapy: overall use—exposure to any regimen; oral treatment—conjugated oestrogens with or without progestogens; transdermal treatment—transdermal oestradiol with or without progestogens; unopposed treatment; and opposed treatment. For each regimen the risk associated with current use was compared with risk in non-users. The effect of duration of use was assessed among current users. Duration was categorised as less

Table 1 Exclusions (n=382) among 674 potential cases of venous thromboembolism

Reason for exclusion	No excluded
Diagnosis not confirmed	109
Superficial phlebitis or cellulitis	66*
Other unrelated diagnosis†	29
Neoplasm	15
Cardiac disease	2
History of venous thromboembolism	9
Recent fracture or injury	16
Recent hospitalisation	15
Recovering from surgery	94
Venous thromboembolism during hospitalisation	20
Information not available	7

*Includes one case excluded in the validation process.

†Rupture of Baker's cyst; thrombosis in arm; arterial embolism; portal vein thrombosis; dural sinus thrombosis.

Table 2 Potential risk factors and venous thromboembolism

	No of cases	No of controls	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Age (years):				
50-60	76	4449	1.0	1.0
61-70	101	3383	1.8 (1.3 to 2.4)	2.1 (1.5 to 2.9)
>70	115	2168	3.1 (2.3 to 4.2)	3.7 (2.6 to 5.1)
Varicose veins or superficial phlebitis:				
No	248	9600	1.0	1.0
Yes	44	400	4.3 (3.0 to 6.0)	3.6 (2.6 to 5.1)
Oophorectomy:				
No oophorectomy or hysterectomy	250	8711	1.0	1.0
Unilateral or hysterectomy, or both	29	1067	1.0 (0.6 to 1.4)	0.9 (0.6 to 1.4)
Bilateral with or without hysterectomy	13	222	2.0 (1.1 to 3.7)	1.7 (0.9 to 3.1)
Body mass index (kg/m ²):				
10-25	41	2785	1.0	1.0
26-50	98	3355	2.0 (1.4 to 2.9)	2.0 (1.4 to 2.9)
Not known	153	3860	2.7 (1.9 to 3.9)	3.3 (2.3 to 4.9)
Smoking:				
Never smoker	128	4218	1.0	1.0
Current or former smoker	56	1688	1.1 (0.8 to 1.5)	1.2 (0.9 to 1.7)
Not known	108	4094	0.9 (0.7 to 1.1)	0.6 (0.4 to 0.8)

*From a model including all the variables in addition to use of hormone replacement therapy and calendar year.

than six months of use; six months to one year; and more than one year. The effect of dose of oestrogens was assessed in current users of conjugated oestrogens or transdermal treatment, either unopposed or opposed, aggregated in a single group of users. Oestrogen dose was categorised as: low dose—users of 0.625 mg of oral conjugated oestrogens, or 25 µg or 50 µg of transdermal oestradiol; and high dose—users of 1.25 mg of conjugated oestrogens or 100 µg of transdermal oestradiol. Information on duration of treatment and type of regimen was not available for some cases and controls; these were excluded from the corresponding analysis.

Adjusted odds ratios and 95% confidence intervals were estimated using unconditional multiple logistic regression. Models were adjusted for age, history of varicose veins or superficial phlebitis, oophorectomy status, body mass index, smoking, and calendar year.

Table 3 Venous thromboembolism and current use of hormone replacement therapy*

Use of hormone replacement therapy	No of cases	No of controls	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI) [†]
Non-use	243	8446	1.0	1.0
Current use	37	1179	1.1 (0.8 to 1.6)	2.1 (1.4 to 3.2)
Duration of treatment [‡] :				
1-6 Months	14	195	2.5 (1.4 to 4.4)	4.6 (2.5 to 8.4)
6 Months-1 year	8	176	1.6 (0.8 to 4.4)	3.0 (1.4 to 6.5)
>1 Year	13	773	0.6 (0.3 to 1.0)	1.1 (0.6 to 2.1)
Oestrogen dose [‡] :				
Low [§]	21	704	1.0 (0.7 to 1.6)	2.1 (1.2 to 3.4)
High [¶]	6	186	1.1 (0.5 to 2.6)	2.4 (1.0 to 5.6)
Type of regimen [‡] :				
Unopposed	11	392	1.0 (0.5 to 1.8)	1.9 (1.0 to 3.8)
Opposed	25	780	1.1 (0.7 to 1.7)	2.2 (1.4 to 3.5)
Route of administration [‡] :				
Oral conjugated oestrogens	20	659	1.1 (0.7 to 1.7)	2.1 (1.3 to 3.6)
Transdermal oestradiol	7	232	1.0 (0.5 to 2.2)	2.1 (0.9 to 4.6)

*Past users (12 cases and 375 controls) not included in this analysis.

[†]Adjusted for age, history of varicose veins or superficial phlebitis, bilateral oophorectomy, body mass index, smoking, and calendar year.

[‡]Information not available on duration of treatment in 2 cases and 35 controls, oestrogen dose in 1 control, and type of regimen and route of administration in 1 case and 7 controls.

[§]0.625 mg for oral conjugated oestrogens; 25 µg and 50 µg for transdermal oestradiol.

[¶]1.25 mg for oral conjugated oestrogens; 100 µg for transdermal oestradiol.

Regression analyses were conducted with the LOGISTIC procedure of SAS release 6.08.¹²

Results

Among the 292 cases of idiopathic venous thromboembolism, 37 (13%) women were current users of hormone replacement therapy. Among controls, current use was found in 1179 women (12%). Use of hormone replacement therapy was strongly inversely related to age. In the age group 50 to 60, 34% (26/76) of cases and 23% (1009/4449) of controls were current users of hormone replacement therapy. After age 60, 5% (11/216) of cases and 3% (170/5551) of controls were current users. The occurrence of venous thromboembolism, on the other hand, increased substantially among older women (table 2). Venous thromboembolism was also positively associated with history of varicose veins or superficial phlebitis, bilateral oophorectomy, and body mass index higher than 25 kg/m² (table 2). The crude odds ratio for venous thromboembolism in current users compared with non-users was 1.1 (95% confidence interval 0.8 to 1.6) (table 3). After adjustment for potential confounding factors, in particular the negative confounding by age, the risk among current users was 2.1 (1.4 to 3.2) (table 3). The risk associated with past use of hormone replacement therapy was 1.4 (0.6 to 3.6).

The risks remained practically the same when different age cut offs were used. No effect on the odds ratios was observed after other potential risk factors (hypertension, hypercholesterolaemia, diabetes) were controlled for, or after the analysis was restricted to women with known body mass index and smoking status. Also, defining current use as within 30 days or 60 days before the index date yielded similar odds ratios (2.1 (1.3 to 3.2) and 2.0 (1.3 to 3.1) respectively).

The increased risk of thromboembolism was restricted to women who had taken hormone replacement therapy for one year or less. The adjusted odds ratios for current users who started treatment within six months or between six months and one year before the index date were 4.6 (2.5 to 8.4) and 3.0 (1.4 to 6.5), respectively (table 3). The odds ratio for current users with more than one year of treatment was 1.1 (0.6 to 2.1).

The effect of dose of oestrogens was examined among current users of conjugated oestrogens or transdermal treatment, either unopposed or opposed. The odds ratio for low dose users was 2.1 (1.2 to 3.4) and for high dose users was 2.4 (1.0 to 5.6) (table 3). The odds ratios for unopposed and opposed use were 1.9 (1.0 to 3.8) and 2.2 (1.4 to 3.5), respectively. For users of oral preparations the odds ratio was 2.1 (1.3 to 3.6) and for those using transdermal treatment the odds ratio was 2.1 (0.9 to 4.6) (table 3).

The risk of pulmonary embolism was 1.9 (1.0 to 3.9) and that of deep venous thrombosis 2.2 (1.4 to 3.6). Seven of the 97 cases of pulmonary embolism and one of the 195 cases of deep venous thrombosis were fatal (case fatality rates of 7.2% and 0.5% respectively). The overall case fatality rate was 2.7%. When we restricted the analysis to the 236 cases with a recorded code for treatment with oral anticoagulants after the episode of thromboembolism, the results were practically the same. The odds ratio for current users

was 2.2 (1.4 to 3.5). For current users with six months or less of treatment the odds ratio was 5.0 (2.6 to 9.6), and for those with six months to one year of use it was 3.3 (1.5 to 7.4).

Discussion

In this study, current use of hormone replacement therapy was associated with a twofold increase in the risk of idiopathic venous thromboembolism. The risk was restricted to the first year of treatment among current users; after one year of treatment the risk was similar to that of non-users. Risk factors for venous thromboembolism (such as age, history of varicose veins or superficial phlebitis, bilateral oophorectomy, obesity, or smoking) did not explain the increased risk. No great oestrogen dose-response was found among current users of conjugated oestrogens or transdermal oestradiol, either with or without progestogens. No major differences in risk were found between users of unopposed and opposed treatment, and between users of oral and transdermal preparations.

These results indicate that in women aged 50-79 who do not use hormone replacement therapy the risk of idiopathic venous thromboembolism is around 1.3 per 10 000 women per year. Among current users of hormone replacement therapy this risk would be increased by a factor of 2.1. This would result in one or two additional cases of venous thromboembolism among 10 000 women using hormone replacement therapy during one year.

Internal validity

In the present study, hormone replacement therapy was associated with venous thromboembolism only after adjustment for potential risk factors. Among these, age was the factor that produced the largest change in the crude odds ratio (about 82%). This negative confounding arises from the positive association between venous thromboembolism and age and the lower use of hormone replacement therapy among older women. Modelling age in different number of categories and cut off limits had little effect on estimates of risk.

The lack of information on body mass index in over 40% of the study subjects could have introduced some bias because of incomplete control of confounding. Although exclusion of women with no information on body mass index led to the same results, some residual confounding cannot be completely discarded.

Non-differential misclassification could be present if women not truly having thromboembolism were included as cases, independent of their exposure status. This could result in an underestimation of the risk of venous thromboembolism. During validation of the identified cases, however, we found that the diagnosis of thromboembolism was not confirmed in only one of the 30 patients reviewed. This level of misclassification is likely to introduce little bias in our estimates of risk.

In this study, women with a recorded history of venous thromboembolism or with other risk factors for thromboembolism were excluded. However, since many practices included in the General Practice Research Database started entering data routinely only at the beginning of the 1990s, historical medical infor-

mation could be incompletely recorded for some patients. History of thromboembolic events is a risk factor for venous thromboembolism, and women with a history could be less likely to receive hormone replacement therapy. This could result in an underestimated relative risk, but this bias would probably be small since, as reflected in many published reviews, there was no awareness during the study period that hormone replacement therapy could affect the risk of venous thromboembolism.

Duration of current use of hormone replacement therapy could be measured only from the date the patient records were computerised. We minimised the potential impact of this missing information on long-term treatment by grouping duration greater than one year in a single category.

One of the concerns in observational studies looking at the effect of replacement oestrogens is the potential for selection bias. Several studies have shown that women who choose to use hormone replacement therapy are healthier than non-users.^{13 14} In a recent study, users of hormone replacement therapy had a better premenopausal cardiovascular risk factor profile than non-users.^{15 16} This type of bias, if present in our study, would underestimate the risk of venous thromboembolism among users of hormone replacement therapy. However, the study was restricted to women without cardiovascular and other chronic diseases. In addition, when we adjusted for hypertension, hypercholesterolaemia, and diabetes, the risk of venous thromboembolism remained unchanged.

On the other hand, women using hormone replacement therapy, like women using oral contraceptives, might be subject to referral or diagnostic bias,¹⁷ which would overestimate the risk of venous thromboembolism. However, the similar risk among patients with deep venous thrombosis and pulmonary embolism, a more serious clinical diagnosis, together with the similar results obtained after restricting the analysis to cases with documented anticoagulant treatment, operate against the presence of a major bias.

Other studies

To the best of our knowledge, this is the largest study examining the association between hormone replacement therapy and the risk of venous thromboembolism. Results from this study are consistent with those of three recent epidemiological studies, conducted in different populations, with different methodologies, which show a twofold to fourfold increase in risk among current users of hormone replacement therapy.⁶⁻⁸ One of these studies was a cohort study from the nurses' health study including 68 cases of pulmonary embolism during a total of 633 817 person years of follow up.⁶ The risk of pulmonary embolism was twice higher among current users than among non-users, with a slightly increased risk during the first five years of use. The other studies were two case-control studies. One was conducted in the United Kingdom and included 103 cases of venous thromboembolism.⁷ The other study used data from the United States and included 42 cases.⁸ Results from these two studies were practically identical. Current use of hormone replacement therapy was associated with a relative risk of 3.5; the risk almost doubled during the

Key messages

- Recent epidemiological studies have shown a twofold to fourfold increased risk of venous thromboembolism among postmenopausal women using hormone replacement therapy
- This population based case-control study further examined the risk of idiopathic venous thromboembolism associated with the use of hormone replacement therapy, in the population of the General Practice Research Database
- Overall, there was a twofold relative risk of venous thromboembolism associated with current use of hormone replacement therapy
- The risk seemed to be restricted to users in their first year of treatment; after this period the risk was similar to that of non-users
- This study indicates that between one and two cases of idiopathic venous thromboembolism per 10 000 women per year could be attributable to current use of hormone replacement therapy

first year of treatment; and a dose-response relation for oestrogen was found in both studies.

Results from these studies together with those from our study, consistently show a small increase in the risk of idiopathic thromboembolism associated with current use of hormone replacement therapy. This new evidence has been reviewed by the Committee on Safety of Medicines in the United Kingdom, which recently produced revised guidelines for doctors.¹⁸

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A PATIENT WHO CHANGED OUR LIVES

It all began with a small lump

In the early 1950s my husband and I, not long qualified, were working in a rural Essex practice. Our education at the end of the war had been scamped and included little on infectious diseases. Such postgraduate teaching as we had was entirely in teaching hospitals and had little relevance.

Late one Saturday night a young farmer came to the door: a Scotsman whose family had migrated to East Anglia in the depressed 1930s. He had little time for doctors, but had this nasty thing on his hand. He was leaving for Aberdeen at four the next morning to stay with his sister, who had a young baby: was it infectious? One of his cows had had a piece of turnip stuck in its throat and he had pulled it out. Perhaps he had scratched his hand on a tooth.

I looked at it with horror: a bulging lesion about 1 cm across, not painful, no inflammation, completely black. Having read books about old time farming and medicine, I had no doubt what it was. I fled to my big textbook of medicine, fairly new but probably a pre-war text. "There is no treatment for anthrax," it said. "The patient remains conscious to the end."

I didn't know what to do, but I knew a man who did. I rang Dr Pilsworth, our friendly and helpful public health laboratory chief, at his home in Southend. "Don't worry," he said, "it certainly sounds like

anthrax—send me a swab. But it responds to penicillin: give him some ointment."

This was one of the "last straws" which led my husband and me to realise that general practitioners had got to pull themselves up by their bootstraps and (with the College of General Practitioners) organise their own teaching. In a few years we had over 400 general practitioner discussion groups meeting regularly to listen to tape slides together, and the Graves Medical Audiovisual Library grew into a huge international organisation which took over a great part of our lives. The first tape, in 1957, was on "The GP and the public health laboratory" by Dr Pilsworth.

And the farmer? Oh yes, he got better. But his sister, a nurse, told him that his doctor was very oldfashioned. Nobody was using penicillin ointment nowadays.

Valerie Graves is a retired general practitioner in Lexden, Essex

We welcome filler articles of up to 600 words on topics such as *A memorable patient*, *A patient who changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.