GX2343

National University of Ireland, Galway

Master of Medical Science

Spring Examination 2001

Medical Informatics

Dr. Peter Cantillon

11.30am – 1.00pm

You must answer **all questions in Section A** and **two out of 3 questions in Section B.**

- Section A contributes 70 marks
- Section B contributes 30 marks

Section A: Critical Appraisal **70 Marks**

Read the paper supplied with this examination paper and answer the following questions

a) Describe the paper provided in terms of its design, methods used and key results.

b) List your major criticisms of this paper, then discuss each criticism in turn.

c) What kind of research questions is the study design used in this paper normally used to answer?

d) What are the common problems associated with this type of study design?

e) Could alternative study design(s) have been used to answer the research question? If so, outline very briefly how you might carry out such a study

Section B: Electronic sources of evidence **30 Marks**

(Answer any two questions out of the three questions listed below)

a) Write short notes on bibliographic and value-added medical databases **(15 Marks)**

b) Explain briefly what the following terms mean: (i) Internet Service Provider, (ii) Internet Browser, (iii) MeSH terms and (iv)Boolean operators.
(15 Marks)

c) Write short notes on three different categories of search engine
(15 Marks)

Articles

Risk of venous thromboembolism in users of hormone replacement therapy

Edel Daly, Martin P Vessey, Michael M Hawkins, Jeffrey L Carson, Parimala Gough, Sally Marsh

Summary

Background The association between current use of oral contraceptives and increased risk of venous thromboembolism (VTE) has been firmly established. Although data-sheets for hormone replacement therapy (HRT) carry similar warnings as regards VTE, evidence of an association is inconclusive. We carried out a hospital-based case-control study to investigate whether current use of HRT is associated with VTE.

Methods We screened all women aged 45–64 years admitted to hospitals in the area of the Oxford Regional Health Authority with a suspected diagnosis of VTE between February, 1993, and December, 1994. We recruited 81 cases of idiopathic VTE and 146 hospital controls with disorders of eyes, skin, ears, respiratory and alimentary tracts, kidneys, bones, and joints, and trauma; controls were matched to cases for age-group and date and district of admission. To increase the study power, an additional 22 cases of idiopathic VTE and 32 hospital controls admitted before February, 1993, were recruited retrospectively. Participants were questioned about medical and gynaecological history, use of oral contraceptives and HRT, use of other drugs within the previous 3 months, and lifestyle and socioeconomic characteristics. Detailed diagnostic data were extracted from the notes of eligible cases. Matched analyses, adjusted for body-mass index, socioeconomic group, and history of varicose veins, were undertaken by conditional logistic regression.

Findings 44 (42·7%) cases and 44 (24·7%) controls were current users of HRT. The adjusted odds ratio for VTE in current users of HRT compared with non-users (never-users and past users combined) was 3·5 (95% CI 1·8–7·0; p<0·001). No association was found with past use, and risk appeared to be highest among short-term current users (adjusted likelihood ratio test of trend in odds ratios across different durations of current use, p=0·011).

Interpretation Current HRT use is associated with risk of VTE. The increased risk may be concentrated in new users. The number of extra cases appears to be only about one in 5000 users per year. These findings need to be weighed against the probable benefits of long-term treatment, including reductions in risks of osteoporotic fracture and coronary heart disease, and the probable modest increase in risk of breast cancer.

Lancet 1996; **348:** 977–80

See Commentary page 972

University of Oxford, Department of Public Health and Primary Care, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE, UK
(E Daly BA, Prof M P Vessey MD FRS, J L Carson MD, P Gough BA, S Marsh SRN); **and Childhood Cancer Research Group, Oxford** (M M Hawkins DPhil)

Correspondence to: Ms E Daly

Introduction

Most studies linking the use of oestrogen to increased risk of venous thromboembolism (VTE) have been carried out in young women in relation to use of oral contraceptives.[1] Hormone replacement therapy (HRT) is not generally believed to carry a similar risk in postmenopausal women. Although none of the studies to address this issue has found a significant increase in VTE associated with HRT,[2–5] each lacked power to detect important risks. The *British National Formulary*[6] states that the evidence of an increased thrombotic risk associated with HRT is questionable, but lists active thrombophlebitis or thromboembolic disorders as contraindications to treatment. Similarly, although a working party of the UK Royal College of Obstetricians and Gynaecologists on prophylaxis against thromboembolism concluded that there was insufficient evidence to suggest that HRT is associated with an increased risk of VTE, their report acknowledged the need for further research.[7]

Our study was undertaken to investigate a possible association between current use of HRT and the risk of idiopathic deep-vein thrombosis (DVT) and pulmonary embolism (PE). The protocol was based on that of a case-control study to examine the association between oral-contraceptive use and VTE in young women.[8]

Patients and methods

Cases

Cases were recruited between February, 1993, and December, 1994, from hospitals in the area of the Oxford Regional Health Authority (as defined before April, 1994) by twice-weekly screening of all relevant wards. Eligible cases were women aged 45–64 years with a suspected diagnosis of PE, DVT, or both. Women with a history of PE, DVT, stroke, or myocardial infarction, and those with a history within the previous 6 weeks of surgery, pregnancy, trauma, or illness necessitating bed rest for longer than 1 week were ineligible for inclusion. One case died before she could be interviewed and was excluded.

Detailed diagnostic data were extracted from the notes of eligible cases. On the basis of signs and symptoms and the results of investigations, diagnoses were classified as definite, probable, possible, or other.[8]

PE was classified as definite if established by a ventilation/perfusion scan or angiogram. The classification was probable PE if there was no good evidence of an alternative diagnosis and if any three of the following were reported: haemoptysis; pleuritic chest pain; shortness of breath of sudden onset; syncope with tachypnoea; electrocardiographic (ECG) pattern, chest radiographic changes, or arterial blood gas concentrations compatible with the diagnosis; other compatible clinical signs (pleural rub, raised jugular venous pressure, abnormal heart sounds); compatible perfusion scan or matched defect seen with ventilation/perfusion scan. PE was classified as possible if there was no good evidence of an alternative diagnosis and any two of the nine signs, symptoms, or investigations listed under probable PE were reported.

DVT was classified as definite if venography, duplex scanning, or radioisotope studies confirmed the presence of a DVT. The classification was probable DVT if there was no good evidence of

	Cases (n=103)	Controls (n=178)
Age (years)*	53·9 (5·9)	53·9 (5·6)
Number who had undergone hysterectomy	31 (30·1%)	54 (30·3%)
Body-mass index (kg/m²)*	27·6 (5·8)	26·0 (4·6)
Number reporting history of varicose veins	29 (28·2%)	27 (15·2%)
Number reporting history of superficial thrombophlebitis	13 (12·6%)	0
Number who had ever used oral contraceptives	55 (53·4%)	101 (56·7%)
Number who smoked during 3 months before admission	28 (27·2%)	47 (26·6%)
Number in socioeconomic group I or II*	23 (22·4%)	57 (32·8%)

*Mean (SD). Smoking status not known for 1 control, body-mass index for 1 case and 2 controls, socioeconomic group for 4 controls.

Table 1: **Characteristics of VTE cases and controls**

an alternative diagnosis, and swelling and induration extended above the knee, and when any two of the following were reported: tenderness on palpation of affected limb; increased superficial temperature of limb; engorgement of superficial veins; doppler ultrasound scan compatible with the diagnosis or equivocal venogram result (the latter was not found in any of our cases). When swelling and induration did not extend above the calf, and in the absence of any other likely cause for the presenting signs and symptoms, a case diagnosis was classified as probable DVT if three of the four signs, symptoms, or investigations listed above were reported. DVT was classified as possible if no good evidence of an alternative diagnosis was reported, and when swelling and induration extended above the knee, and when no more than one of the four signs, symptoms, or investigations listed above was reported. When swelling and induration were confined to the calf, and in the absence of any other likely cause for the presenting signs and symptoms, a case diagnosis was classified as possible if two of the four signs, symptoms, or investigations listed above were reported.

For both PE and DVT, any cases not satisfying any of these criteria were classified as 'other'.

Cases who had diagnoses of both PE and DVT were classified, for the purposes of analysis, to the diagnosis of greater certainty. When both diagnoses were judged equally certain, cases were classified as DVT since this disorder usually precedes PE.

Controls

Controls were recruited from among women admitted to hospital with a diagnosis judged to be unrelated to HRT use in this age-group. Acceptable diagnoses included diseases of the eye, ear, skin, respiratory and alimentary tracts, kidneys, bones, and joints, or trauma. For recruitment, wards were screened in a random order. Up to two controls were recruited per case, matched by 5-year age-group, district of admission, and date of admission (between 2 weeks before and 4 months after the admission date of the corresponding case). The exclusion criteria applied for cases were also applied for controls.

Retrospective recruitment of cases and controls

To increase the study power, additional participants were recruited retrospectively. Details were obtained of all women aged 45–64 years, discharged between April, 1990, and March, 1993, with a first diagnosis of PE or DVT or any of the acceptable control diagnoses, from hospitals in the area of the Oxford Regional Health Authority. Because of financial constraints, only the first 26 such cases (plus 36 matching controls) from Oxford and Kettering were recruited to the study.

Interviews

Participants were interviewed while still in hospital by one of two research nurses. Cases who were discharged before they could be interviewed (23%) were interviewed at home, as were their matched controls. All retrospectively recruited participants were interviewed at home. During the interview the women were questioned about medical and gynaecological history, past and present use of HRT, past and present use of oral contraceptives, use within the past 3 months of other drugs, estimated height and weight, smoking habit, alcohol intake, and occupation. Photographs of currently available HRT and oral-contraceptive preparations were used during the interview to aid recall.

	n	% of group	
		Current use of HRT	Ever use of HRT
Cases	103	42·7	52·4
Control diagnostic group			
Eye and ear diseases	20	20·0	25·0
Respiratory diseases	16	18·8	37·5
Alimentary diseases	26	23·1	38·5
Renal diseases	18	27·8	44·4
Skin diseases	13	38·5	53·8
Bone and joint disorders	49	22·4	34·7
Hip and wrist fractures	8	37·5	37·5
Other fractures	19	26·3	42·1
Non-fracture trauma	9	22·2	77·8
All controls	178	24·7	39·9

Table 2: **Prevalence of current use and ever use of HRT among cases and control subgroups**

Exclusions

Women were excluded after interview if they reported a history of cancer of the breast, ovary, endometrium, or other recent (diagnosed in the year before the current hospital admission) or active cancer; a history of serious heart disease; or use of anticoagulants or oral contraceptives (four women) in the month before admission. Decisions to exclude were made by an investigator unaware of case or control status and exposure to HRT.

Definitions

Women were classified as current HRT users if they had used the treatment at any time in the month preceding their admission to hospital. One user who did not know the preparation name was included in all analyses except those relating to the type of preparation. Four controls who had stopped using HRT in anticipation of their hospital admission were classified as current users. Tibolone, a synthetic compound with oestrogenic, progestagenic, and androgenic properties, was regarded as HRT, but data for women using this drug are presented separately in the subgroup analyses. Because of evidence of an association between current but not past use of oral contraceptives and risk of VTE,[8] we considered a priori that the most appropriate reference group in all analyses was non-users of HRT (past users and never-users combined), subject to confirmation of no evidence of risk associated with past use in the data from this study. Body-mass index was categorised based on quintiles of control group values. Each woman was assigned to one of six socioeconomic groups based on her partner's occupation, or her own if she was single or if her partner's occupation was not given.[9] Women were classified as current smokers if they had smoked during the 3 months before hospital admission.

Analysis

Conditional logistic regression analyses of matched data[10] were undertaken. Body-mass index, a history of varicose veins, and

Comparison	Cases	Controls	Matched odds ratio (95% CI)	
			Unadjusted	Adjusted*
Relative to never-users				
Never use	49	107	1·0	1·0
Past use	10	27	0·8 (0·4–1·7)	1·1 (0·5–2·6)
Current use	44	44	2·9 (1·5–5·4)	3·6 (1·8–7·3)
Relative to non-users				
Non-use	59	134	1·0	1·0
Current use	44	44	3·0 (1·6–5·6)†	3·5 (1·8–7·0)†

*For body-mass index, history of varicose veins, and socioeconomic group.
†Likelihood ratio test of a difference in risk of VTE between non-users and current users of HRT, p<0·001.

Table 3: **Odds ratios of VTE in relation to current HRT use**

socioeconomic group were judged a priori to be potential confounding variables and were included in adjusted models if they produced a change of at least 5% in the estimated odds ratio of VTE associated with HRT.[11]

Results

108 cases (69 with DVT and 39 with PE) and 232 controls satisfied all inclusion criteria. The proportions of cases with definite, probable, possible, and other diagnostic certainty ratings were 73%, 20%, 4%, and 3% for DVT, and 33%, 51%, 10%, and 5% for PE. Cases in the 'other' category were excluded from all further analyses. Participants without matching cases or controls were also excluded. 103 cases and 178 controls remained; of these, 22 cases and 32 controls had been recruited retrospectively. The characteristics of the study population are given in table 1. As expected, mean body-mass index was higher among cases than controls, reflecting the increased risk of VTE in overweight people. Higher proportions of cases than controls reported histories of varicose veins and superficial thrombophlebitis, whereas a lower proportion were classified in the higher socioeconomic groups.

Overall 44 (42·7%) cases and 44 (24·7%) controls were current users of HRT (table 2). A matched analysis yielded an odds ratio for VTE associated with current HRT use of 3·0 (95% CI 1·6–5·6) compared with non-users (never-users and past users combined; table 3). Each of the potential confounding variables (body-mass index, a history of varicose veins, and socioeconomic group) produced a change of at least 5% in the estimated risk of VTE associated with HRT.[11] After adjustment for these factors, the odds ratio was 3·5 (1·8–7·0).

Estimated odds ratios in relation to duration of current episode of use are shown in table 4. The odds ratios

Comparison	Cases	Controls	Matched odds ratio (95% CI)	
			Unadjusted	Adjusted*
Non-users†	59	134	1·0	1·0
Duration of current episode of use (months)				
1–12	14	10	4·1 (1·5–10·8)	6·7 (2·1–21·3)
13–36	16	12	3·2 (1·4–7·5)	4·4 (1·6–11·9)
37–60	4	11	1·2 (0·3–4·5)	1·9 (0·5–7·8)
≥61	10	11	2·7 (1·0–7·2)	2·1 (0·8–6·1)
Composition of HRT‡				
Oestrogen only	22	21	3·1 (1·4–6·5)	3·2 (1·4–7·4)
Oestrogen and progestagen	20	20	4·0 (1·6–9·6)	5·3 (1·9–14·6)
Tibolone	1	3	0·6 (0·1–6·4)	1·1 (0·1–13·0)
Oestrogen dose§				
Lower-dose oestrogen	17	14	4·1 (1·7–10·0)	3·7 (1·3–10·2)
Higher-dose oestrogen	16	16	3·4 (1·4–8·4)	6·6 (2·2–19·6)
Unknown dose	9	10	2·6 (0·9–7·4)	2·4 (0·8–7·1)
Implant	1	1	5·1 (0·3–88·9)	2·3 (0·1–65·6)
Tibolone	1	3	0·6 (0·1–6·2)	1·2 (0·1–14·3)
Route of administration				
Oral therapy	37	32	3·6 (1·8–7·2)	4·6 (2·1–10·1)
Transdermal therapy	5	8	2·2 (0·7–7·5)	2·0 (0·5–7·6)
Implant	1	1	3·9 (0·2–66·4)	2·1 (0·1–50·2)
Tibolone	1	3	0·6 (0·1–6·6)	1·1 (0·1–13·2)

*For body-mass index, history of varicose veins, and socioeconomic group. †Never-users and past users, baseline category throughout. ‡Unknown for 1 case. §Lower dose includes oral preparations containing 0·625 mg conjugated equine oestrogens, 1 mg oestradiol/oestradiol valerate, or 1·5 mg piperazine oestrone sulphate; and includes transdermal preparations delivering 50 μg oestradiol per 24 h. Higher dose includes oral preparations containing 1·25 mg conjugated equine oestrogens or 2 mg oestradiol/oestradiol valerate; and includes transdermal preparations delivering 100 μg oestradiol per 24 h.

Table 4: **Odds ratios of VTE in relation to current HRT use by duration of current episode of use, type of preparation, oestrogen dose, and route of administration**

associated with short-term use of HRT are higher than those for longer durations, and this effect was strengthened somewhat by adjustment for confounding. There was evidence that the logarithms of the odds ratios decreased linearly with increasing duration of current use; the adjusted likelihood ratio test for such an effect yielded a p value of 0·011. Risk estimates according to oestrogen dose, type of preparation, and route of delivery are also shown in table 4. Among current users, there was no significant difference in the risk of VTE between high-dose and low-dose preparations, between oral and transdermal therapy, or between unopposed oestrogen and combined oestrogen-progestagen therapy.

In analyses by certainty of case diagnosis the unadjusted estimated odds ratios for VTE associated with current HRT use were higher for the definite (2·9 [95% CI 1·3–6·5]) and probable (4·7 [1·3–17·4]) categories, than for the possible (1·4 [0·3–7·5]) category. Various multivariate analyses were undertaken to investigate the effects of exclusion of women with certain characteristics that might lead to biased results. There were no important differences in the odds ratios associated with current HRT use, or in the pattern in relation to duration of current use, when we excluded all women with a history of superficial thrombophlebitis; controls with an index diagnosis of fracture; cases with a diagnostic rating of probable or possible; and retrospectively recruited participants. However, in the last two subgroup analyses, we were unable to obtain risk estimates relating to duration of use, since there were too few data for a regression equation to be fitted.

Discussion

The results of our study and those of Jick and colleagues[12] suggest a possible causal relation between current HRT use and idiopathic VTE. This interpretation is supported by results from a study of exogenous hormones in relation to risk of PE by Grodstein and colleagues.[13] In our study, risk of VTE seemed to be highest among short-term users, whereas no association was seen with past use. Although the magnitude of estimated risk was greater among users of higher-dose preparations than among users of lower-dose preparations, this difference was not significant. Similarly, we found no significant difference in risk between users of oral and transdermal therapy, or between users of unopposed oestrogen and combined oestrogen-progestagen therapy.

At least three case-control studies and one small clinical trial have investigated the possible association between HRT and VTE.[2–5] The sample sizes ranged between 17 and 121 cases, and the studies found non-significant relative risks between 0·7 and 1·8. In each, no more than six cases had been exposed to HRT, whereas our results are based on 44 HRT-exposed cases. In the clinical trial,[4] no cases of serious embolic disease occurred among 84 long-term hospital inpatients treated with HRT for 10 years, whereas one case of VTE occurred among the untreated group. The largest study to date found a relative risk of 0·79 (95% CI 0·30–2·08).[5] However, VTE had occurred while the women were in hospital for another reason in more than a third of cases, 21% of cases had a history of previous VTE, and the average age of the participants was high (65 years).

Preferential referral and diagnosis of exposed cases is a potential source of bias in observational studies.[14] Analysis

by certainty of case diagnosis in our study yielded risk estimates that were lowest in the possible category for both DVT and PE; the confidence intervals were wide, however, because of small numbers in these subgroups. Exclusion of cases without a definite diagnosis did not reveal any appreciable differences in the risk estimates associated with HRT use.

The problem of recall bias is a common criticism of case-control studies. Since the exposure of interest in this study was use of HRT in the month before admission, we would expect very little recall bias among prospectively recruited subjects, most of whom were interviewed while still in hospital. Although recall bias might be of some concern in relation to the participants who were recruited retrospectively (20%), use of photographs of packets of all available HRT preparations during the interview should have aided recall. In addition, the relative risk of VTE in association with current HRT use was essentially unchanged when the retrospectively recruited subjects were excluded.

The use of hospital patients as controls in epidemiological studies of postmenopausal oestrogen has been criticised, since such women may be less likely to be using HRT; however, prevalence of use among controls in this study was similar to that among women attending for breast screening in Oxfordshire.[15]

15% of controls recruited to this study were patients who had sustained fractures. Although women with osteoporotic fracture may be less likely to have used HRT,[16] a previous diagnosis of osteoporosis might increase their chances of treatment. Of the controls with fractures, less than a third had fractures of the hip, wrist, or vertebrae, types that may indicate underlying osteoporosis. None had a previous diagnosis of osteoporosis and the proportion using HRT did not differ significantly from that in other controls (table 2). Exclusion of all controls with an index diagnosis of fracture from our analyses did not materially change the results.

A history of previous DVT or PE was an exclusion criterion. However, a significantly higher proportion of cases than of controls reported a history of thrombophlebitis (table 1). Treatment prescribed for past episodes of thrombophlebitis included antibiotics and non-steroidal anti-inflammatory drugs rather than anticoagulants, which suggests that the thrombophlebitis was superficial rather than deep. 54% of these women had ever used HRT, compared with 44% of all other women; the proportions for current use were 46% and 31%, respectively. These findings suggest that doctors do not generally regard a history of superficial thrombophlebitis as a contraindication to HRT. Our results did not change substantially when women with a history of thrombophlebitis were omitted from the analysis.

On the basis of these results and on regional population statistics,[17] the annual rate of idiopathic VTE per 100 000 women aged 45–64 years is estimated to be 27·4 among HRT users and 10·9 among non-users, which gives an annual total of 16·5 cases per 100 000 that may be attributed to HRT. This risk may be entirely acceptable to women using HRT in the short-term for the relief of menopausal symptoms, especially to those without other risk factors for VTE. For long-term HRT users, these findings need to be weighed against the probable benefits of long-term treatment, including reductions in risks of osteoporotic fracture[18] and coronary heart disease,[18,19] and the probable slight increase in risk of breast cancer.[20] Since mortality from venous thromboembolism is low, our findings are unlikely to change the overall balance of benefits and risks of long-term treatment substantially.[21] Further research is needed to establish whether HRT is contraindicated in the presence of other risk factors for venous thromboembolism, including obesity, recent surgery, immobilisation, and thrombophilic disorders.

We thank Schering Health Care Ltd, Novo Nordisk Pharmaceuticals, and the Knott Family Trust for their financial support of this work. MPV holds a research consultancy with Novo Nordisk Pharmaceuticals. JLC was a Fogarty Senior International Fellow at the University of Oxford.

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