Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review

The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study

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Summary

Combined oral contraceptives, oral hormone replacement therapy and thrombophilias are recognised risk factors for venous thromboembolism in women. The objective of this study was to assess the risk of thromboembolism among women with thrombophilia who are taking oral contraceptives or hormone replacement therapy, conducting a systematic review and meta-analysis. Of 201 studies identified, only nine met the inclusion criteria. Seven studies included pre-menopausal women on oral contraceptives and two studies included peri-menopausal women on hormone replacement therapy. For oral contraceptive use, significant associations of the risk of venous thromboembolism were found in women with factor V Leiden (OR 15.62; 95%CI 8.66 to 28.15); deficiencies of antithrombin (OR 12.60; 95%CI 1.37 to 115.79), protein C (OR 6.33; 95%CI 1.68 to 23.87), or protein S (OR 4.88; 95%CI 1.39 to 17.10), elevated levels of factor VIIIc (OR 8.80; 95%CI 4.13 to 18.75); and factor V Leiden and prothrombin G20210A (OR 7.85; 95%CI 1.65 to 37.41). For hormone replacement therapy, a significant association was found in women with factor V Leiden (OR 13.16; 95%CI 4.28 to 40.47). Although limited by the small number of studies, the findings of this study support the presence of interaction between thrombophilia and venous thromboembolism among women taking oral contraceptives. However, further studies are required to establish with greater confidence the associations of these, and other, thrombophilias with venous thromboembolism among hormone users.

Introduction

Oral oestrogen use in women has been associated with increased risk of venous thromboembolism. In premenopausal women, the risk of venous thromboembolism has been shown to increase by about two to six-fold during the use of combined oral contraceptives, and in peri- and post-menopausal women, two to four-fold during the use of hormone replacement therapy (1).

Heritable thrombophilias include deficiencies of antithrombin, protein C and protein S; and common genetic mutations such as factor V Leiden and the prothrombin G20210A mutation and the thermolabile variant (C677T) of the methylene tetrahydrofolate reductase (MTHFR) gene (where association appears much weaker) (2). Other relatively common thrombophilias with a combination of heritable and acquired components include elevated plasma factor VIIIc (3), hyperhomocysteinaemia (4)

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and acquired activated protein C resistance (5). Few studies have investigated the risk of venous thromboembolism in thrombophilic women who use hormone therapies. A recent UK guideline from the Royal College of Obstetricians and Gynaecologists on hormone replacement therapy and venous thromboembolism highlighted the lack of evidence in this area, and suggested that hormone replacement therapy should not be recommended in women with high risks such as Type 1 antithrombin deficiency, with combined defects, or additional risk factors for venous thromboembolism (6).

The objective of this study was to evaluate and summarise the evidence for the association between thrombophilia and increased risk of venous thromboembolism in patients who were prescribed oral contraceptives or hormone replacement therapy.

Methods

Search strategy

An extensive search was carried out by two independent reviewers (OW, LR) on all major electronic databases: Medline 1966 to June 2003, BIDS (EMBASE) 1980 to June 2003, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL) 1982 to June 2003, Cochrane Database of Systematic Reviews 1998 to June 2003, Database of Reviews of Effectiveness (DARE) 1995 to June 2003 and Kings Fund, UK (last accessed June 2003). Relevant keywords related to thrombophilia (thrombophilia, hypercoagulability, factor V, activated protein C resistance, prothrombin, antithrombin, protein C, protein S, hyperhomocysteinaemia, factor VIII, lupus anticoagulant, and anticardiolipin antibodies) combined with hormones (oral contraceptives, hormone replacement therapy, oestrogen, progestin, medroxyprogesterone, SERMS, and raloxifene), were used (as MeSH terms and text words) to capture all potentially relevant studies. Only articles published in English were retrieved. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original studies. Hand searching the abstracts of recent thrombosis conferences and the references of all studies meeting the reference criteria was also carried out.

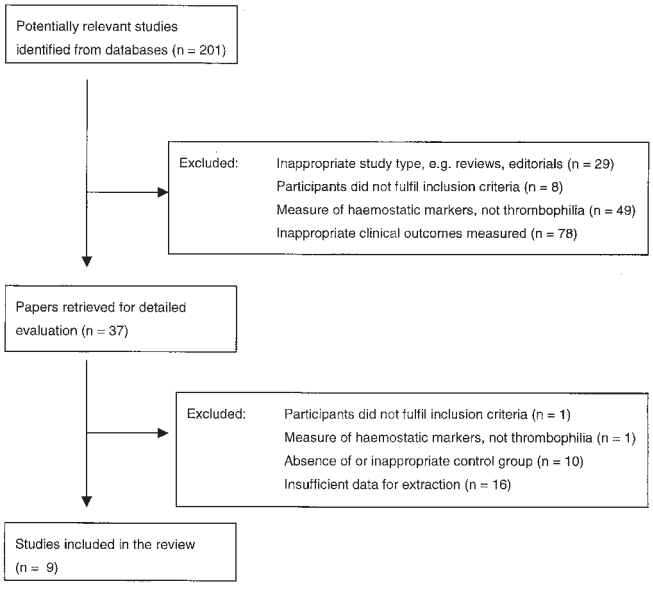

Figure 1: Selection of studies for systematic review.

Inclusion and exclusion criteria

All prospective and retrospective studies were included in the review if they met the following criteria:

- study population included those prescribed oral contraceptives or hormone replacement therapy
- clinical outcomes included measures of incidence of venous thromboembolism events and/or mortality
- extractable data that defined categorically the presence or absence of any thrombophilic defects were available.

Data extraction

Data from studies meeting the inclusion criteria were reviewed and extracted into pre-piloted data extraction forms independently by the two reviewers during which the quality of the forms was also assessed. This systematic review included a variety of study types. In order to maintain a consistency of reporting, a validated generic checklist designed for quantitative studies was used to assess the quality of all the studies included in the review (7). This checklist originally included 14 criteria, however, one of which referred to random allocation of treatment and another referred to blinding of subjects. These were considered not applicable to observational studies and were excluded from the checklist; therefore, the final checklist consisted of 12 items. These items are consistent with the recommendations from the Centre for Reviews and Dissemination (CRD) (8) and the consensus statement of meta-analysis reporting of observational studies in epidemiology (9). Any disagreement relating to inclusion of studies, data extraction or quality assessment between the reviewers was resolved by discussion.

Data synthesis

The outcomes of interest included all confirmed venous thromboembolism incidence measures, including deep vein thrombosis (DVT), pulmonary embolism (PE), and mortality. Each study included in the review was summarised according to its odds ratio, stratified by hormone use and individual thrombophilic defects, both alone and in combination. Odds ratios greater than one indicate an increased risk of venous thromboembolism-events or mortality associated with hormone use and thrombophilia. Where appropriate, meta-analysis was carried out and pooled odds ratios were calculated based on the random effect model (DerSimonian and Laird), which accounts for inter-study variations and provides a more conservative estimate of effect than the fixed effect model. Potential sources of heterogeneity were investigated and assessed using the standard chi-square test (χ^2). Sensitivity analysis was carried out to assess the robustness of the results of the meta-analysis. All analyses were performed using RevMan 4.1 (Cochrane Collaboration, Oxford, UK).

Results

Of 201 studies identified from the searches, only nine studies met the inclusion criteria (Fig. 1). No studies of the MTHFR mutation were found.

Combined oral contraceptives

Six case-control studies and one retrospective cohort study on combined oral contraceptives met the inclusion criteria for the review (Table 1). Venous thromboembolism events observed in 1127 combined oral contraceptive users were compared with 1767 non-users. The methodological qualities of the studies were relatively consistent (Table 1). Only one study described blinded assessment of outcomes.

The results of the meta-analysis (Fig. 2) showed strong associations between the use of oral contraceptives and throm-

Table 1: Description of studies on thrombophilia and oral contraceptive use included in the review.

Source and Type of Study	Participants	Hormones	Thrombophilia	Outcome Measures	Results	Quality Criteria
Andersen et al (1998); Denmark (13) Case-control study	Cases (n = 67) – women with spontaneous DVT or PE identified from discharge records. Controls (n = 134) – blood donors from the same region, age-matched (2:1).	Oral contraceptives – classified into third generation and other (i.e. first and second generation and progestogen-only pill) OC. Information on OC use (three months prior to admission for cases) was obtained from hospital records, telephone interviews and self-administered questionnaires.	FVL, AT, PC, PS	VTE events Thrombotic events were confirmed at diagnosis by phlebography, ultrasound, perfusion lung scan echocardiography or when the event led to treatment with heparin or anticoagulants.	The risk of VTE in the presence of heritable thrombophilia (including FVL, AT, PC and PS) was similar for both third generation OC users and users of other OC (OR 52.5; 95%CI 3.7 to 738.1 and OR 63.3; 95%CI 6.2 to 648.4, respectively).	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Partial 7 = No 8 = Yes 9 = Yes 10 = Yes 11 = Yes 12 = Yes
Bloemenkamp et al (1999); The Netherlands (16) Case-control study	Cases (n = 155) – pre-menopausal women with confirmed first deep vein thrombosis identified from the records of anticoagulation clinics. Controls (n = 169) – friends and acquaintances, or partners of other patients at the clinic, with no history of deep vein thrombosis, matched for age.	Oral contraceptives – classified into non-current OC use and current OC use. Information on OC use (one month prior to event for cases) was obtained from personal interviews.	High FVIII (≥150 IU/dl)	DVT First episode of proven DVT diagnosed by established objective methods.	Both OC use and high FVIII levels were shown to be associated with increased DVT risk (OR 3.8, 95% CI 2.4 to 6.0 and OR 4.0, 95% CI 2.0 to 8.0). The presence of both factors had an additive effect, resulted in OR 10.3 (95%CI 3.7 to 28.9).	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Yes 7 = Yes 8 = Yes 9 = Yes 10 = Partial 11 = Yes 12 = Yes
Legnani et al (2002); Italy (15) Case-control study	Cases (n = 301) – women who had at least one venous thromboembolism event during reproductive age. Controls (n = 650) – healthy women of reproductive age from the same geographical area.	Oral contraceptives – classified according to the type of progestin into second generation and third generation. Information on OC use was obtained from personal interviews.	AT, PC, PS, APCR, FVL, Prothrombin G20210A	VTE events Objectively confirmed DVT (confirmed by compression ultrasonography or venography) of the lower limb, with and without PE (confirmed by ventilation perfusion lung scan).	A strong interaction between OC use and the presence of either FVL (OR 41.0, 95% CI 13.5 to 125) or prothrombin G20210A (OR 58.6, 95% CI 12.8 to 276) mutations was observed. The risk of VTE in OC users who had both mutations was significantly increased (OR 86.5, 95% CI 10.0 to 747).	1 = Yes 2 = Yes 3 = Partial 4 = Yes 5 = Yes 6 = Yes 7 = No 8 = Yes 9 = Yes 10 = Partial 11 = Yes 12 = Yes
Martinelli et al (1999); Italy (11) Case-control study	Cases (n = 148) – women with first objectively documented DVT. Control (n = 277) – healthy women who were friends or partners of referred patients in the same 3-year study period.	Oral contraceptives – classified into first, second and third generation. Information on OC use at the time of thrombosis, i.e. until two weeks or less before the thrombotic event (cases) or time of sampling (controls) was recorded.	Thrombophilia screen: prothrombin G20210A, FVL, antiphospholipid syndrome, AT, PC, PS, LA and anticardiolipin antibodies.	DVT First, objectively documented episode of DVT of the lower extremities.	The most prevalent circumstantial risk factor in patients and the only one observed in controls was OC use, conferred a 6-fold increased risk of thrombosis. The risk increased to OR 16.3 (95% CI 3.4 to 79.1) and OR 20.0 (95% CI 4.2 to 94.3) in OC users with prothrombin G20210A and FVL, respectively, indicating a multiplicative interaction between the genetic risk factors and OC use.	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Yes 7 = No 8 = Yes 9 = Yes 10 = Partial 11 = Yes 12 = Yes
Santamaria et al (2001); Spain (10) Retrospective cohort study	Cohort (n = 325) women from 97 families with at least two family members identified as carriers of one or more thrombophilic factors (AT, PC, PS, FVL, Prothrombin G20210A).	Oral contraceptives – first, second and third generation. Information was obtained by questionnaires filled out during an appointment or by a telephone interview.	AT, PC, PS, FVL, Prothrombin G20210A	VTE events Deep vein thrombosis with or without pulmonary embolism. Standard objective diagnostic procedures were used for all symptomatic women.	The risk of VTE in prothrombin carriers using OC was three-fold higher (95%CI 1.3 to 6.8) than that in non-carriers. Carriers of FVL taking OC showed OR 1.4 (95%CI 0.6 to 3.3).	1 = Yes 2 = Yes 3 = Partial 4 = Yes 5 = Yes 6 = Partial 7 = No 8 = Yes 9 = Yes 10 = Partial 11 = Yes 12 = Yes

Quality criteria: 1 = study question sufficiently described; 2 = design evident and appropriate to answer study question; 3 = method of subject selection (and comparison group selection, if applicable) is described and appropriate; 4 = subject (and comparison group, if applicable) characteristics sufficiently described; 5 = outcome and (if applicable) exposure measure(s) well defined and robust to measurement.misclassification bias; 6 = sample size appropriate; 7 = blinding of investigators; 8 = analysis described and appropriate; 9 = some estimate of variance for the main results/outcomes; 10 = controlled for confounding; 11 = results reported in sufficient detail; 12 = do the results support the conclusions. The studies by Bloemenkamp et al (1999) and Vandenbroucke et al (1994) in the table refer to the same study population, but reported the VTE risks of high FVIIIc and FVL, respectively.

Table 1: Continued

Source and Type of Study	Participants	Hormones	Thrombophilia	Outcome Measures	Results	Quality Criteria
Spannagl et al (2000); Germany (14) Case-control study	Cases (n = 80) – women with DVT or PE. Controls (n = 406) – women randomly sampled by computer form the population-based BATER study database. Up to six controls were randomly matched per case, by age group.	Oral contraceptives – current use and no use (never or past use) at the time of event or interview. Information on OC use was obtained by self-administered questionnaires.	FVL	VTE events VTE diagnosed if clinical signs were present and confirmed by imaging tests and/or treated with anticoagulants.	Matched, adjusted OR for idiopathic VTE in women without and with FVL who used OC were 4.1 (95% CI 2.1 to 7.8) and 10.2 (95% CI 1.2 to 88.4), respectively. The adjusted OR for FVL carrier was 2.0 (95% CI 1.0 to 4.4). The OR for women with FVL and OR versus no FVL and no OC was 10.2 (95% CI 3.8 to 27.6).	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Partial 7 = No 8 = Yes 9 = Yes 10 = Yes 11 = Yes 12 = Yes
Vandenbroucke et al (1994); The Netherlands (12) Population-based case-control study	Cases (n = 155) – pre-menopausal women with confirmed first deep vein thrombosis identified from the records of anticoagulation clinics. Controls (n = 169) – friends and acquaintances, or partners of other patients at the clinic, with no history of deep vein thrombosis, matched for age.	Oral contraceptives – classified into non-current OC use and current OC use. Information on OC use (one month prior to event for cases) was obtained from personal interviews.	FVL	DVT First episode of proven DVT diagnosed by established objective methods.	The risk of thrombosis among OC users was increased four-fold (RR 3.8, 95% CI 2.5 to 6.0). The risk of thrombosis among FVL carriers was increased eight-fold (RR 7.9, 95% CI 3.2 to 19.4). Compared with non-OC users not carrying the mutation, the risk of thrombosis among those with both risk factors was increased more than 30-fold (RR 34.7, 95% CI 7.8 to 154).	1 = Yes 2 = Yes 3 = Partial 4 = Partial 5 = Yes 6 = Yes 7 = No 8 = Yes 9 = Yes 10 = Partial 11 = Yes 12 = Yes

Quality criteria: 1 = study question sufficiently described; 2 = design evident and appropriate to answer study question; 3 = method of subject selection (and comparison group selection, if applicable) is described and appropriate; 4 = subject (and comparison group, if applicable) characteristics sufficiently described; 5 = outcome and (if applicable) exposure measure(s) well defined and robust to measurement.misclassification bias; 6 = sample size appropriate; 7 = blinding of investigators; 8 = analysis described and appropriate; 9 = some estimate of variance for the main results/outcomes; 10 = controlled for confounding; 11 = results reported in sufficient detail; 12 = do the results support the conclusions. The studies by Bloemenkamp et al (1999) and Vandenbroucke et al (1994) in the table refer to the same study population, but reported the VTE risks of high FVIIIc and FVL, respectively.

bophilia (alone and in combination), and venous thromboembolism. The odds ratios for oral contraceptive use and the risk of venous thromboembolism ranged between 1.32 and 4.90. Overall, the odds of developing venous thromboembolism among oral contraceptive users were almost three times greater than that of non-users (OR 3.10; 95% CI 2.17 to 4.42). However, significant (p = 0.003) heterogeneity was present among the studies.

The risk associated with thrombophilia and venous thromboembolism in this study population was also calculated (Fig. 2). Positive associations between factor V Leiden and venous thromboembolism were reported in six studies (10–15) and a pooled odds ratio of 3.78 (95%CI 2.22 to 6.42) was observed. Although no significant heterogeneity was detected (p = 0.14), the inconsistency among the study results was moderately large (Fig. 2). The odds of developing venous thromboembolism in those with protein S deficiency was approximately five times (OR 5.31; 95%CI 2.48 to 11.37) that of those without the deficiency. This finding was based on data from two studies (10, 13). No evidence of heterogeneity (p = 0.57) was detected between the two studies. Individual studies reported the risks of venous thromboembolism with protein C deficiency (OR 2.45; 95%CI 1.18 to 5.11) and elevated levels of factor VIIIc (OR 4.56; 95%CI 2.05 to 10.15) (10, 16). The increase in risks associated with the combined defects of factor V Leiden and prothrombin G20210A were reported in two studies (10, 15), and meta-analysis gave a pooled odds ratio of OR 4.03 (95%CI 1.01 to 16.01). These studies showed no evidence of heterogeneity (p = 0.59). The prothrombin G20210A mutation and antithrombin deficiency were described in three (10, 11, 15) and two studies (10, 13), respectively. Increased risks were observed with prothrombin G20210A (OR 1.34; 95%CI 0.81 to 2.23) and antithrombin deficiency (OR 3.18; 95%CI 0.82 to 12.29), the odds ratios were not statistically significant. No association was observed with the combined defect of prothrombin G20210A and protein C deficiency (OR 0.80; 95%CI 0.08 to 7.82). However, data were only available from one study (10).

A supra-additive effect for risk of venous thromboembolism was observed between the use of oral contraceptives and thrombophilias. The odds of developing venous thromboembolism in those who had both risk factors were substantially amplified compared with either of the risk factors considered alone. The most significant increased risk was observed with factor V Leiden and use of oral contraceptives (OR 15.62; 95%CI 8.66 to 28.15), five times that observed with either risk factor in isolation. Similar, but less pronounced effects were also observed in oral contraceptive users who had deficiencies of antithrombin, or protein C. The combination of risk factors resulted in odds four (OR 12.60; 95%CI 1.37 to 115.79) and two times (OR 6.33; 95%CI 1.68 to 23.87) that observed with either risk factor in isolation, respectively. Test for heterogeneity was non-significant (p = 1.00 and p = 0.40, respectively). Meta-analysis of two studies (10, 15) showed that the use of oral contraceptives doubled the risk of those with combined thrombophilic defects of factor V Leiden and prothrombin G20210A but no oral contraceptive use (OR 7.85; 95%CI 1.65to 37.51). No significant heterogeneity (p = 0.21) was detected among the results. One study reported an association between elevated levels of factor VIIIc in combination with oral contraceptive use and venous thromboembolism (OR 8.8; 95%CI 4.13 to 18.75) (16). No significant association was observed with prothrombin G20210A (OR 6.09; 95%CI 0.81 to 45.64); or with combined defects on prothrombin

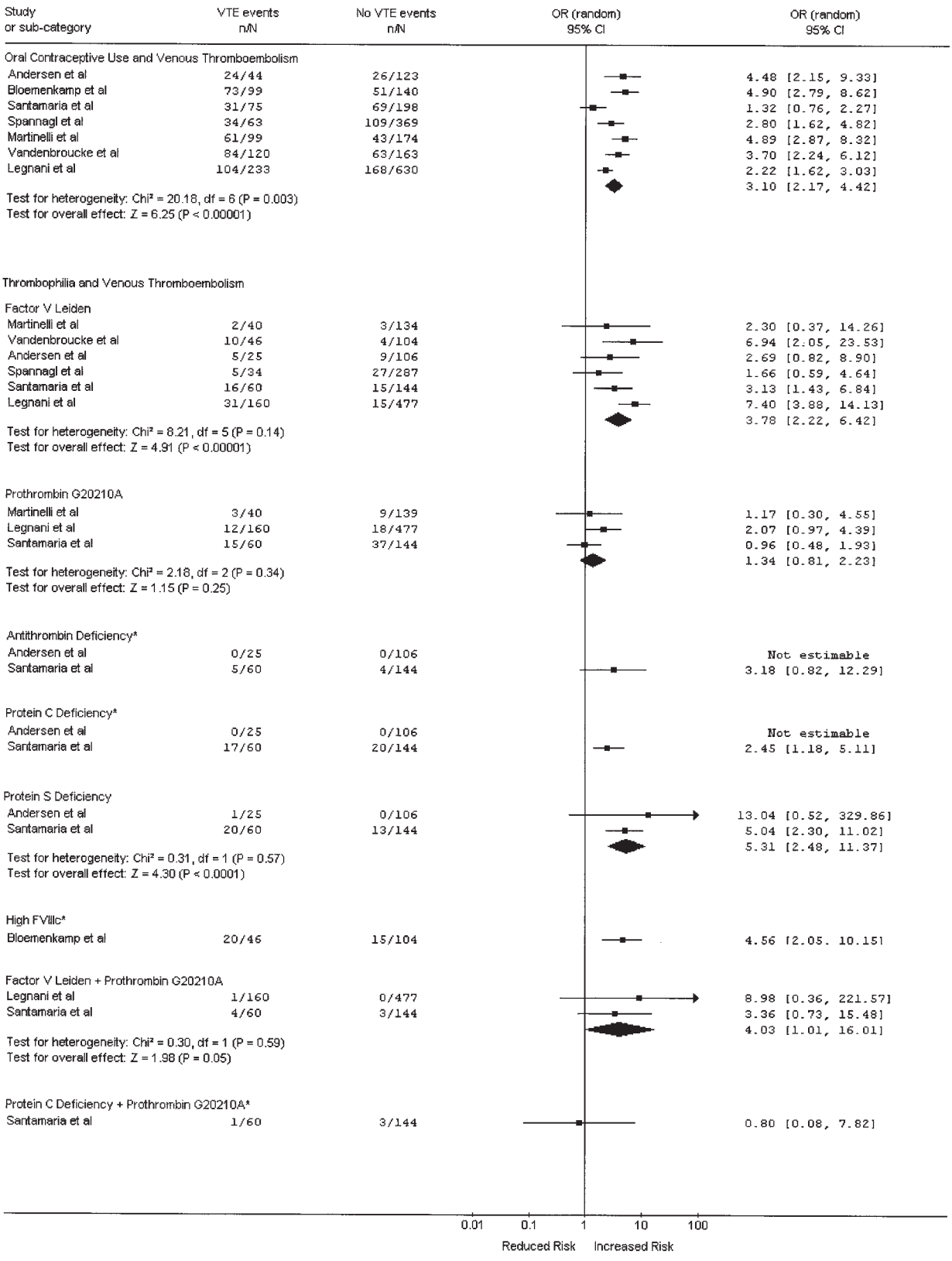

Figure 2: Odds ratios for the risk of venous thromboembolism in studies of selected thrombophilias and oral contraceptive use. Data from only one study was available; no metaanalysis was performed.

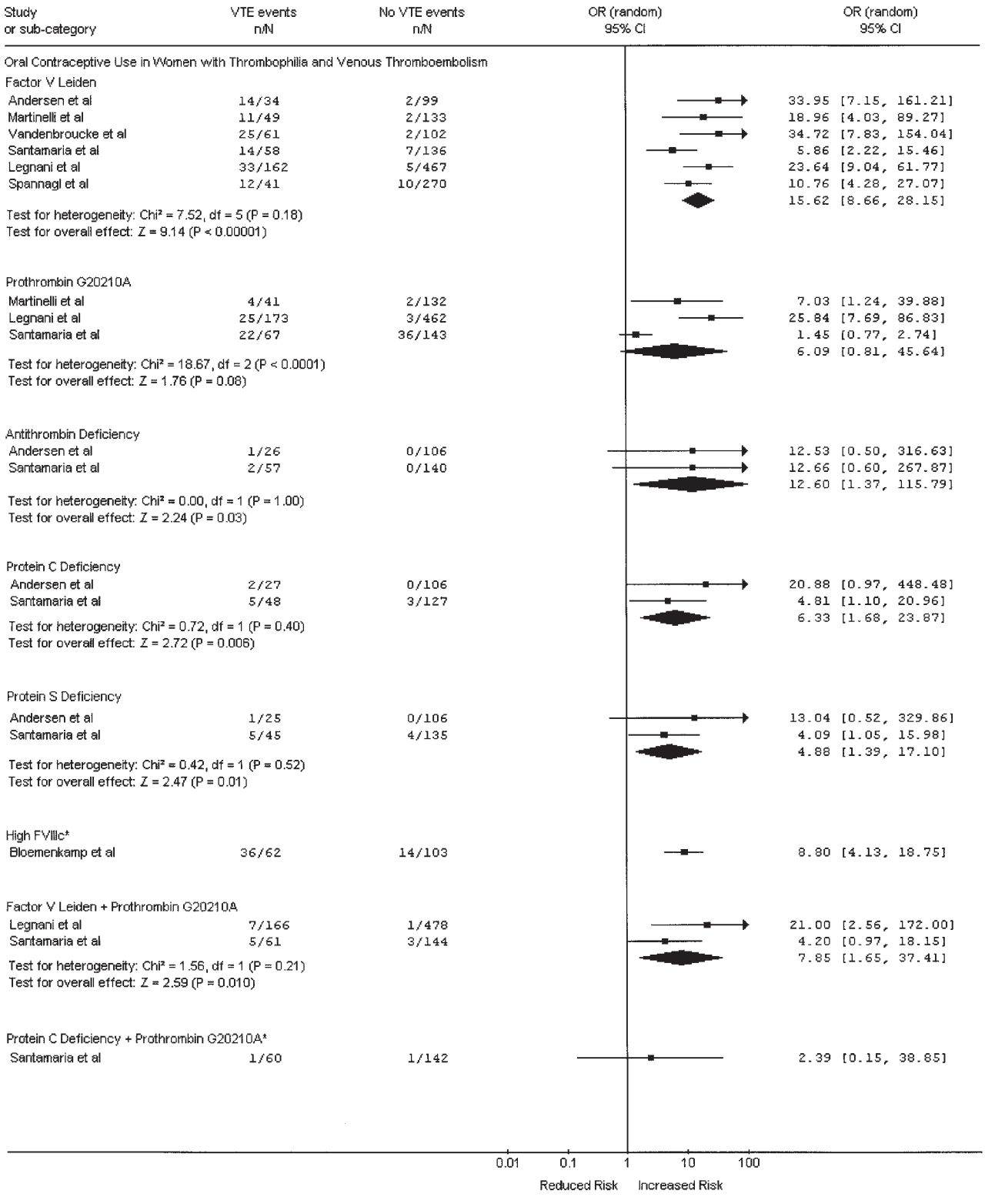

Figure 2: Continued. Data from only one study was available; no metaanalysis was performed.

G20210A and protein C (OR 2.39; 95% CI 0.15 to 38.85) with oral contraceptive use. A pooled odds ratio of 4.88 (95%CI 1.39 to 17.10) was observed with protein S deficiency and the use of oral contraceptives. However, this was lower than risk observed with protein S deficiency in isolation (OR 5.31; 95%CI 2.48 to 11.37).

Sensitivity analysis was carried out to explore the heterogeneity and inconsistencies of the results of the studies included in

Table 2: Description of studies on thrombophilia and hormone replacement therapy use included in the review.

Source and Type of Study	Participants	Hormones	Thrombophilia	Outcome Measures	Results	Quality Criteria
Herrington et al (2002); US [17] Nested case-control study	Participants of the HERS and ERA trial. Postmenopausal women, <80 years with documented coronary artery disease. Cases (n = 48) – women who had a thrombotic event during the trial. Controls (n = 112) – those who did not have a thrombotic event.	Hormone replacement therapy – participants in the HERS trial received oral conjugated equine oestrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg daily. Participants in the ERA trial received oral conjugated equine oestrogen 0.625 mg, oestrogen plus medroxyprogesterone acetate 2.5 mg.	FVL	VTE events A diagnosis of DVT was confirmed by venography, impedance plethysmography, or ultrasound. A diagnosis of PE was confirmed by a segmental or larger ventilation/perfusion mismatch on a nuclear lung scan or an intraluminal filling by pulmonary angiography.	Factor V Leiden was present in 8/48 cases and 7/112 controls (OR 3.3, 95% CI 1.1 to 9.8). In non-FVL carriers, the risk associated with HRT use was significantly increased (OR 3.7, 95% CI 1.4 to 9.4). However, in FVL carriers, the risk associated with HRT use increased nearly six-fold (OR 5.7, 95% CI 0.6 to 53.9). The OR for women with FVL assigned to HRT compared with non-carriers given placebo was 14.1 (95% CI 2.7 to 72.4).	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Yes 7 = Yes 8 = Yes 9 = Yes 10 = Yes 11 = Yes 12 = Yes
Rosendaal et al (2002); UK [20] Case-control study	Cases (n = 77) – women admitted with a main diagnosis of a first episode of DVT or PE. Controls (n = 163) – women admitted for diagnoses unrelated to thrombosis and HRT. Up to two controls were chosen per case, matched by 5-year age group, district and date of hospitalisation.	Hormone replacement therapy (all types) – current users were defined as the use of HRT at any time in the month prior to hospital admission.	Prothrombotic mutations: FVL, prothrombin G20210A	VTE events Idiopathic deep vein thrombosis and pulmonary embolism, classified as definite (objectively confirmed), probable, possible or other.	Among the cases, 51% were receiving HRT at the time of thrombosis compared with 24% of the control group (OR 3.3, 95% CI 1.8 to 5.8). A prothrombotic mutation (FVL or prothrombin G20210A) was observed in 23% of the cases compared with 7% of controls (OR 3.8, 95% CI 1.7 to 8.5). None of the prothrombin G20210A carriers used HRT. Women who had FVL and HRT use had a 15-fold increased risk of thrombosis (OR 15.5, 95% CI 3.1 to 7.7).	1 = Yes 2 = Yes 3 = Yes 4 = Yes 5 = Yes 6 = Yes 7 = No 8 = Yes 9 = Yes 10 = No 11 = Yes 12 = Yes

Quality criteria: 1 = study question sufficiently described; 2 = design evident and appropriate to answer study question; 3 = method of subject selection (and comparison group selection, if applicable) is described and appropriate; 4 = subject (and comparison group, if applicable) characteristics sufficiently described; 5 = outcome and (if applicable) exposure measure(s) well defined and robust to measurement.misclassification bias; 6 = sample size appropriate; 7 = blinding of investigators; 8 = analysis described and appropriate; 9 = some estimate of variance for the main results/outcomes; 10 = controlled for confounding; 11 = results reported in sufficient detail; 12 = do the results support the conclusions

the meta-analysis. All the analyses were repeated using a fixed effect model, however, there was little change in the results. The effect of study type was also investigated by restricting the analysis to case-control studies and excluding the only cohort study (10) in the analysis. This resulted in a modest increase in the estimated risk of FVL and oral contraceptive use, and the inconsistency among the results reported in the individual studies was removed (OR 19.43; 95%CI 11.42 to 33.06). This restriction also had a significant impact on the analysis on prothrombin G20210A and oral contraceptive use. A significant increase in risk of venous thromboembolism was estimated (OR 15.66; 95%CI 4.44 to 55.18). No evidence of heterogeneity was shown (p = 0.22). These findings are unsurprising; due to potential ascertainment bias, the risks reported in case-control studies have been known to be greater than that reported in cohort studies.

Hormone replacement therapy

Two studies on HRT were included in the review (Table 2). One was a nested case-control study of factor V Leiden (17) from two trials (18, 19). Another case-control study (20) included factor V Leiden and prothrombin G20210A mutation. Only four patients carried prothrombin mutations (two cases and two controls) and none were users of hormone replacement therapy. Therefore, no analysis was carried out for the prothrombin G20210A mutation.

Meta-analysis for factor V Leiden, the use of hormone replacement therapy, and venous thromboembolism events was conducted (Fig. 3). The results reported by both studies were consistent and tests for heterogeneity were non-significant (p = 0.89 hormone replacement therapy, 0.77 factor V Leiden and 0.78 hormone replacement therapy and factor V Leiden). The use of hormone replacement therapy was associated with a three-times increased risk in venous thromboembolism events (pooled OR 3.16; 95%CI 1.90 to 5.23). A similar effect was observed with the presence of factor V Leiden mutation (pooled OR 3.58; 95%CI 1.43 to 8.97). Patients who had both risk factors had much higher risk of developing venous thromboembolism events (pooled OR 13.16; 95%CI 4.28 to 40.47).

Discussion

This review was based on literature reports that women with thrombophilias who take hormones such as oral contraceptives and hormone replacement therapy are at increased risk of developing venous thromboembolism. Based on the current evidence available in the literature, the findings of this study generally support this hypothesis, indicating that certain thrombophilias, in particular factor V Leiden; deficiencies of antithrombin, protein C, or protein S; elevated levels of factor VIIIc and compound heterozygosity for factor V Leiden and prothrombin G20210A increase the risk of venous thromboembolism among users of oral contraceptives; and also that factor V Leiden increases the risk in users of hormone replacement therapy. While we reviewed only studies with hormone users, the odds ratios for the increase in risk of venous thromboembolism were similar to those studies of thrombophilia in the general population (2, 21).

With the exception of antithrombin deficiency, the reported odds ratios for thrombophilic women developing venous thromboembolism during the use of oral contraceptives varied substantially in individual studies. For instance, the reported odds ratios for venous thromboembolism among women with factor V

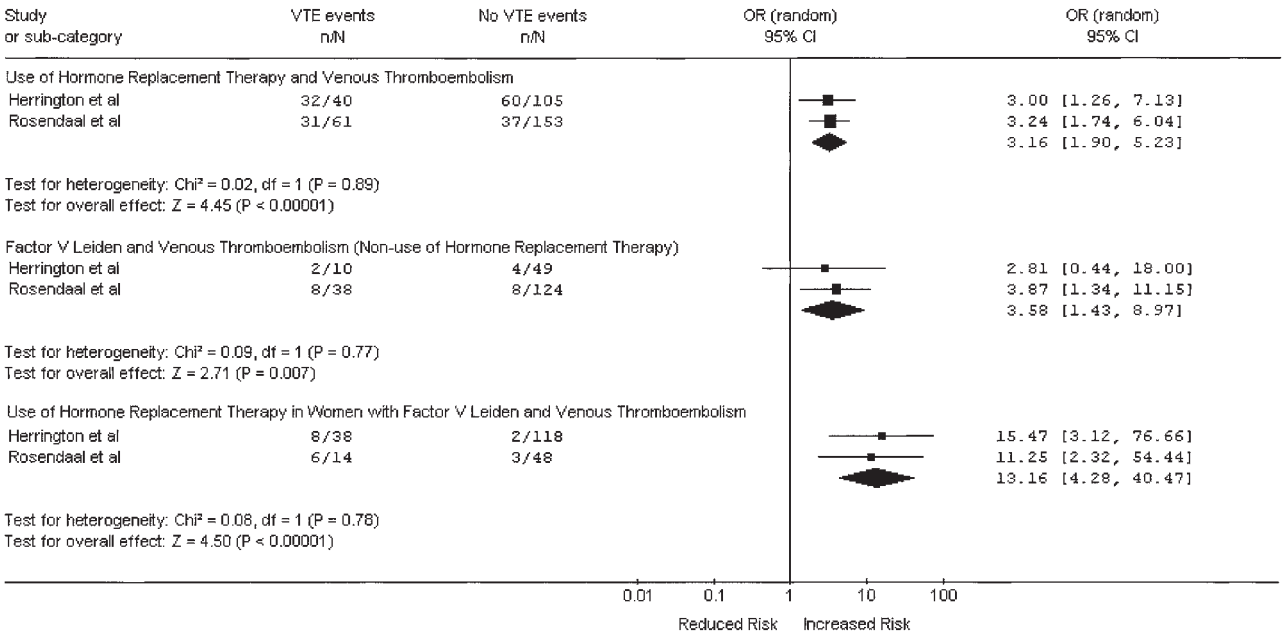

Figure 3: Odds ratios for the risk of venous thromboembolism in studies of selected thrombophilias and hormone replacement therapy use. Data from only one study was available; no metaanalysis was performed.

Leiden who were oral contraceptive users ranged from 5.86 (10) to 34.72 (12). One reason may be different inclusion criteria: the studies of Legnani (15) and Santamaria (10) were performed on women referred for a thrombophilia workup and women with familial thrombophilia respectively; such women may have a higher risk of thrombosis (22). The pooled odds ratio estimated by our meta-analysis was 15.62, substantially less than the most commonly cited odds ratio first reported by Vandenbroucke et al (12). Our result is similar to a previous, smaller meta-analysis of three studies (OR 10.25) (23). This meta-analysis also reported similar results to the present study for prothrombin G20210A (OR 7.14) and for its combination with factor V Leiden (OR 16.97) (23). The variations observed in other thrombophilic defects, such as deficiencies of protein C and protein S and combined thrombophilic defects, may be explained by the study type as the results were pooled from both case-control and cohort studies.

The thrombophilias described in this study represented primarily heterozygous mutations. Four studies did not define the genotypes (11, 13, 14, 17), one study presented summed data for both heterozygous and homozygous mutations (10), two studies excluded all homozygous carriers (12, 15), and one study had no homozygous carriers (20). Separate analysis on individual genotypes was not carried out due to the lack of data. Vandenbroucke et al have estimated, based on a multiplicative effect, that the risk increase for homozygous factor V Leiden among oral contraceptive users may be more than 100-fold (12).

The type of combined oral contraceptive has been shown to be an important factor in determining the risk increase in venous thromboembolism. Third generation oral contraceptives have been shown to incur greater risks than other classes of oral contraceptives (1, 24). Four of the studies included in this review described the distinction between third generation and other oral contraceptives (10, 11, 13, 15), but separate data were presented only in one study (13). Although this study showed that third generation oral contraceptives had a greater effect than other oral contraceptives on the risk of venous thromboembolism (OR 20.9 compared with 7.1), this effect was no longer observed in women with the factor V Leiden mutation. The risk of venous thromboembolism was greater in first and second generation oral contraceptive users compared with third generation oral contraceptives (OR 64.7 compared with 29.6).

Few studies have investigated the relationship between thrombophilias and venous thromboembolism in users of hormone replacement therapy. Since no data were available on thrombophilias other than factor V Leiden, the results of this review have been restricted to women with factor V Leiden, who had a very similar increase in risk of venous thromboembolism in two studies (19, 20). One study, not included in this review due to the lack of extractable data (25) also reported significant increases in the risk of venous thromboembolism in women with high levels of factor IX (OR 2.34), increased resistance to activated protein C (OR 4.06), decreased antithrombin (OR 3.33) or decreased protein C (OR 2.93). The risk of venous thromboembolism in women using transdermal hormone replacement therapy has been shown to be lower than that observed with oral preparations (26–28). However, to date, no data relating to transdermal hormone replacement therapy users with thrombophilia have been presented in the literature.

This systematic review highlights the small number of relevant published studies available for inclusion in meta-analyses. Although only studies published in English were included in this review, it is unlikely that this would result in the exclusion of important studies and the introduction of significant selection bias (29). In addition, the literature search indicated that non-English studies are not particularly prevalent in this area. The majority of

studies identified were case-control studies, which may be biased with regards to selection of controls. The confidence intervals of the estimated odds ratios for thrombophilias such as deficiencies of antithrombin, proteins C or S, and the combined thrombophilic defects among oral contraceptive users are large, and hence the results should be interpreted with caution. Furthermore, comparisons of thrombophilia, the use of oral oestrogen preparations and the risk of venous thromboembolism are indirect. The large observed differences between the venous thromboembolism odds ratios for some thrombophilias, and thrombophilia plus oral oestrogen use, had limited sample size, hence formal analyses were not feasible. We therefore recommend that larger studies, including more thrombophilic patients and controls, are required to provide more reliable estimates. Meanwhile, it seems reasonable to conclude that the interaction of oral contraceptives and factor V Leiden were supra-additive, because the lower 95% CI (8.7) of the meta-analysis exceeds the sum of risks (5.9).

It has been suggested that women might be screened for thrombophilia prior to prescribing hormone preparations, including combined oral contraceptives (30) and hormone replacement therapy (20). However, due to the low incidence of venous thromboembolism in these populations of women, the absolute risk is low and mass screening strategies are unlikely to be effective. Important issues such as absolute risk, acceptability, psychological consequences deriving from the diagnosis of thrombophilia, potential consequences of false positive and false negative results, and economic issues, need all to be taken into account. We are currently preparing a further paper on screening, which addresses some of these considerations.

Abbreviations

DVT – deep vein thrombosis, PE – pulmonary embolism, OC – oral contraceptives, FVL – factor V Leiden, AT – antithrombin deficiency, PC – protein C deficiency, PS – protein S deficiency, VTE – venous thromboembolism, OR – odds ratio, APCR – activated protein C resistance, LA – lupus anticoagulant, HERS – the Heart and Estrogen/Progestin Replacement Study, ERA – the Estrogen Replacement and Atherosclerosis, HRT – hormone replacement therapy.

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