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


CRD summary
This review assessed the association between thrombophilia and increased risk of venous thromboembolism in women taking oral contraceptives or hormone replacement therapy. The authors concluded that an interaction appears to exist between certain thrombophilias and venous thromboembolism among women taking oral contraceptives, and that further research is required. This is an association of risk, hence causality cannot be assumed.

Authors' objectives
To assess the association between thrombophilia and increased risk of venous thromboembolism (VTE) in women taking oral contraceptives (OC) or hormone replacement therapy (HRT).

Searching
Two independent reviewers searched MEDLINE (1966 to June 2003), EMBASE (1980 to June 2003), CINAHL (1982 to June 2003), the Cochrane Database of Systematic Reviews (1998 to June 2003), DARE (1995 to June 2003) and Kings Fund UK (last accessed June 2003) for articles published in the English language; the search terms were reported. Abstracts of recent thrombosis conferences were handsearched, as were the references of studies meeting the eligibility criteria. A list of articles which cited the studies identified by the search was retrieved from the Web of Science database.

Study selection
Study designs of evaluations included in the review
Prospective and retrospective studies were eligible for inclusion.

Specific interventions included in the review
Studies of OC or HRT were eligible for inclusion. Some of the studies noted whether first-, second- or third-generation pills were received.

Participants included in the review
Studies of patients prescribed OC or HRT were eligible for inclusion. The studies needed to provide extractable data categorically defining the presence or absence of any thrombophilic defect.

Outcomes assessed in the review
Studies measuring the incidence of VTE and/or mortality were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion, and any disagreements were resolved through discussion.

Assessment of study quality
A validated generic checklist for quantitative studies was used to assess study quality (see Other Publications of Related Interest). Some of the criteria were: sufficient description of patient characteristics; outcome and exposure well defined and robust to measurement; appropriate sample size; and controlling for confounders. Two of the 14 quality criteria were removed as they were not applicable to the included study designs. Two reviewers independently assessed the quality of the included studies, and any disagreements were resolved through discussion.
Data extraction
Two reviewers independently extracted the data into pre-piloted data extraction forms, and any disagreements were resolved through discussion.

Methods of synthesis
How were the studies combined?
Where appropriate, the studies were combined in a meta-analysis, using the random-effects model of DerSimonian and Laird to derive a pooled odds ratio (OR) and 95% confidence interval (CI). The studies were stratified by hormone use and individual thrombophilic defects.

How were differences between studies investigated?
The chi-squared test was used to assess heterogeneity. Sensitivity analyses were conducted to assess the influence of study type on the pooled results.

Results of the review
Nine studies were included. There were 7 studies (n=2,712) on thrombophilia and OC: 6 case-control studies (two of which reported on the same study population) and 1 retrospective cohort study. There were 2 studies (n=400) on thrombophilia and HRT: 1 case-control study and 1 nested case-control study.

The studies were of relatively consistent methodological quality.

Studies of OC.
The overall odds of developing VTE with OC were nearly three times greater than that in women not taking OC (OR 3.10, 95% CI: 2.17, 4.42). However, there was significant heterogeneity among these studies (P=0.003).

There was a significant association of risk of VTE in women taking OC with factor V Leiden (OR 15.62, 95% CI: 8.66, 28.15) in 6 studies, antithrombin deficiency (OR 12.60, 95% CI: 1.37, 115.79) in 2 studies, protein C deficiency (OR 6.33, 95% CI: 1.68, 23.87) in 2 studies, protein S deficiency (OR 4.88, 95% CI: 1.39, 17.10) in 2 studies, and factor V Leiden and prothrombin G20210A (OR 7.85, 95% CI: 1.65, 37.41) in 2 studies. No significant heterogeneity was reported in any of the meta-analyses.

One study found a significant association of risk of VTE in women with elevated levels of factor VIIIc (OR 8.80, 95% CI 4.13, 18.75).

There was no significant association of risk of VTE in women with prothrombin G20210A alone (3 studies). However, there was significant heterogeneity between these studies (P<0.0001).

One study found no significant association of risk of VTE in women with protein C deficiency and prothrombin G20210A.

There was little change in the results when the analyses were repeated using a fixed-effect model.

Analyses were also repeated by restricting inclusion to case-control studies, by removing one cohort study. A modest increase in the estimated risk of factor V Leiden and OC use was observed in addition to the now consistent results of individual studies and the significant increase in risk of VTE with prothrombin G20210A and OC.

Studies of HRT.
There was a significant association of risk of VTE in women using HRT with factor V Leiden (OR 13.16, 95% CI: 4.28, 40.47) in 2 studies.

Authors' conclusions
The authors concluded that their findings support the presence of interaction between certain thrombophilias and VTE among women taking OC, although this conclusion was limited by the small number of studies. Further studies are required to confidently establish the associations of these and other thrombophilias with VTE among hormone users.

**CRD commentary**
The review had clear inclusion criteria relating to the study design, intervention, participants and outcomes. A comprehensive search was conducted for published and unpublished studies, although the restriction to papers published in English might have led to language bias. Two independent reviewers conducted the study searches and selection, extraction and quality assessment stages, thus reducing the potential for reviewer error or bias. The criteria for assessing the quality of the studies were appropriate, and the results of this assessment were tabulated along with the study details. The studies were appropriately combined according to type of thrombophilia and use of hormones, and heterogeneity between the studies was investigated.

The authors' conclusions reflect their findings, and they also cautioned that the included case-control studies may be biased with regard to the selection of controls. It must be stressed that this is an association of risk and causality cannot be assumed.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that larger studies with more thrombophilic patients and controls are necessary for more reliable estimates.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.