Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis

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CRD summary
This review, which assessed the risk of venous thromboembolism in postmenopausal women using hormone replacement therapy, concluded that transdermal oestrogens may be safer than oral oestrogens. Given the limitations of the included studies and of the review process and data synthesis, the authors’ conclusions may not be reliable. However, their recommendations for further research appear reasonable.

Authors' objectives
To assess the risk of venous thromboembolism (VTE) in postmenopausal women using hormone replacement therapy, taking into account study design, treatment and outcome characteristics, and clinical background.

Searching
MEDLINE was searched from 1974 to 2007 for publications in English; the search terms were reported. In addition, the references of original articles and those of review articles published post-1970 were checked.

Study selection
Studies assessing the risk of VTE from hormone replacement therapy were eligible for inclusion, while studies of contraception were excluded. The included studies used various doses of oral or transdermal oestrogens administered in the previous 1 to 6 months, including 17-β-oestradiol with or without norethisterone acetate, conjugated equine oestrogen alone or in combination with cyclic medroxyprogesterone acetate, consecutive medroxyprogesterone acetate or cyclic micronised progesterone, or esterified oestrogen. The majority of studies included a control group, and reported first time idiopathic deep venous thrombosis or pulmonary embolism as the primary outcome. Clinical events were mostly validated by ultrasonography or lung scanning.

Specific inclusion criteria for the participants and study design were not stated. The included studies were of healthy women, or women with a history of coronary heart disease, VTE, stroke or possible arterial disease, with or without hysterectomy, or factor V Leiden mutation or prothrombin G20210A mutation. The included studies were randomised controlled trials (RCTs) and observational studies (case-control and prospective cohort).

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed separately for RCTs and observational studies. RCTs were assessed on the basis of randomisation and generation of random numbers, blinding, reporting of withdrawals and allocation concealment, and were given a score of between 0 and 5. Observational studies were assessed for the following items: appropriate participant selection methods; reporting of first episode of VTE; use of an objective diagnostic procedure; adequate assessment of menopausal status and hormone therapy; and adequate analysis and adjustment. Cohort studies were also assessed for loss to follow-up. Cohort studies received a score of 0 to 7 and case-control studies a score of 0 to 6.

Two reviewers independently assessed validity and any discrepancies were resolved by consensus.

Data extraction
The number of events for idiopathic or secondary deep vein thrombosis or pulmonary embolism were used to calculate the adjusted relative risks or odds ratios (ORs), with 95% confidence intervals (CIs).

It appears that two reviewers independently extracted the data and any discrepancies were resolved by discussion.
Methods of synthesis
The ORs were pooled according to study design, weighted by the inverse of the variance; a random-effects or fixed-effect model was used, as appropriate. Only cohort studies scoring 6 or higher were included in the meta-analysis. Heterogeneity was assessed using the $\chi^2$ and $I^2$ tests. Subgroup analyses were undertaken by type of hormone therapy, outcome diagnosis and patient characteristics. A sensitivity analysis was conducted by removing studies not reporting the first episode of idiopathic events.

Results of the review
Nine RCTs (n=38,779, range: 140 to 16,608 participants), 7 case-control studies and one prospective cohort study were included. The number of patients included in the observational studies was not reported.

Seven RCTs scored 5 on the validity assessment and two scored 4. Four case-controls scored 6 for validity and three scored 5, and the prospective cohort study scored 7. The duration of follow-up in the RCTs ranged from 0.99 to 7 years.

Oral versus transdermal oestrogen (17 studies).

With the exception of one RCT and one observational study, the remaining studies reported an association between oral oestrogen and increased risk of VTE (OR 2.4, 95% CI: 1.9, 3.0). One study reported an association between increased risk and equine oestrogen, but no data were presented. No associations were reported between increased risk and transdermal oestrogen or esterified oestrogen. Five case-control studies reported a significant association between increased risk of VTE and duration of treatment, with the greatest risk reported for treatment duration up to 1 year (OR 4.0, 95% CI: 2.9, 5.7) compared with treatment for more than 1 year (OR 2.1, 95% CI: 1.3, 3.8, p<0.05). Previous use of hormone therapy (4 observational studies) and use of oral oestrogen alone or in combination with progesterone were not associated with increased risk.

Outcome diagnosis (17 studies).

No significant results were reported for type of VTE and oral oestrogen use. The sensitivity analysis for 7 studies reporting the first episode of idiopathic events showed a substantial increase in risk using oral oestrogen (OR 3.1, 95% CI: 2.3, 4.1), but the results were not significantly altered for studies using transdermal oestrogen.

Results for women at high risk of VTE with the presence of factor V Leiden mutation or prothrombin G20210A mutation were reported in the review, but the studies reported were not identified as eligible for inclusion.

There was significant heterogeneity among observational studies and randomised studies using oral oestrogen (p=0.03), and for studies examining hormone therapy for more than 1 year. The authors also reported other sources of heterogeneity, but no data were presented.

Authors’ conclusions
Risk of VTE is increased with oral oestrogen use, particularly in the first year of treatment, and use of transdermal oestrogen may be safer. Further research is required to examine the differences in risk across different hormone regimens, in particular different types of progestogens.

CRD commentary
The review question was clear, but the supporting inclusion criteria were limited and not always clearly defined. The literature search was also limited to only one electronic database and one other appropriate source. Publications were restricted by language, which may have introduced language bias and, as there was no apparent search for unpublished material, it is possible that relevant papers were missed. Validity was assessed and the included studies appeared to be of a high quality. Details of the validity assessment and data extraction were reported, but not the study selection process, thus the potential for reviewer error and bias cannot be ruled out. Appropriate methods were used to investigate heterogeneity but, as significant heterogeneity was evident for the majority of studies, it may not have been appropriate to pool the results. Although some study details were reported clearly, potentially important clinical information on participant characteristics and details of controls were not provided, which makes it difficult to determine the relevance of the included participants to the review question. Given these considerations about the
reporting in the review, the authors' conclusions should be interpreted with caution since they may not be reliable. However, their recommendations for further research appear reasonable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the route of oestrogen administration may have important clinical implications for the risk of VTE, and the use of transdermal oestrogens improves the benefit and risk profile of hormone replacement therapy.

**Research:** The authors stated that further research is required to assess the risk of VTE using different regimens of transdermal oestrogen and oestrogen combined with progestogens. Further research to assess the effects of genetic factors on risk associated with hormone replacement therapy is also warranted.

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