Effects of non-oral postmenopausal hormone therapy on markers of cardiovascular risk: a systematic review

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CRD summary
This review concluded that potentially unfavourable effects on C-reactive protein and activated protein C were substantially smaller with non-oral hormone therapy than with oral therapy. Non-oral hormone therapy had minor effects on other cardiovascular risk factors. These conclusions reflect the results of the review, but methodological and reporting shortcomings make their reliability difficult to determine.

Authors' objectives
To assess the effects of non-oral administration of postmenopausal hormone therapy on risk markers for atherosclerotic and venous thromboembolic disease.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1980 to April 2006. Search terms were reported. References of identified studies were checked. Studies reported in English, Dutch, German, French or Spanish were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) that compared one or more non-oral hormone therapy regimen with no treatment, placebo or oral hormone therapy in postmenopausal women were eligible for inclusion. Studies were required to have a minimum of 10 women in each trial arm and to report follow-up for at least four weeks. Studies of both women with spontaneous and surgically induced menopause were eligible, as were those of healthy women or those with established cardiovascular disease or specified cardiovascular risk factors.

Most included trials were in healthy women; most others enrolled women with risk factors for coronary heart disease and only a few assessed women with coronary heart disease. Most included trials assessed transdermal hormone therapy using either a patch or a gel; a few used intranasal administration. Hormones administered were transdermal oestrogen alone, transdermal oestrogen and progestogen, transdermal oestrogen combined with oral progestogen, and intranasal equivalents of these combinations. Outcome measures were detailed in the report.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted using standardised forms. Where data were reported in multiple publications, data on the longest follow-up or largest study group were extracted. Percentage changes from baseline were recorded or estimated, graphical presentations were used where necessary. Levels of significance used by study investigators were adopted.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The studies were combined in a narrative synthesis grouped by outcome.

Results of the review
Seventy-six RCTs were included in the review: 71 parallel designs and five crossover trials. Follow-up ranged from four weeks to two years.
**Lipoprotein(a)**: Studies showed a neutral or slightly lowering effect of non-oral hormone therapy on lipoprotein(a) compared with baseline, but not compared with control groups. This was not significantly different from the decrease caused by oral hormone therapy.

**Homocysteine**: Reported changes in homocysteine were non-significant and did not differ from the lack of effect seen with oral hormone therapy.

**Inflammation**: All except two studies of non-oral hormone therapy reported non-significant changes or no changes in C-reactive protein, one showed a significant increase and one a significant decrease. All studies that assessed oral therapy reported significant increases from baseline, which were significantly different to controls in most cases. Changes in cell adhesion molecules appeared to be less pronounced with non-oral therapy than with oral therapy.

**Markers of endothelial dysfunction**: Data on this outcome were limited, but it appeared that changes in markers of endothelial dysfunction were not significant. Endothelin-1 did not show differences between oral and non-oral therapy; there were larger decreases in asymmetric dimethylarginine with oral therapy.

**Anticoagulant proteins**: Changes in antithrombotic proteins were small and mostly non-significant. Where significant changes were found these were usually in relation to baseline rather than to control groups; differences between oral and non-oral groups were not considered to be significant overall.

**Resistance to activated protein C**: Significant increases in resistance to activated protein C were found, although these were considered to be of smaller magnitude than those seen with oral therapy.

**Markers of coagulation**: A significant decrease in factor VII coagulation activity was found during non-oral hormone therapy, while none of the other markers for coagulation showed an overall significant change. There were no significant differences between oral and non-oral groups with the possible exception of prothrombin fragment 1+2, where there may be fewer changes in the non-oral groups.

**Markers of fibrinolysis**: The decreases in total plasminogen activator and total plasminogen activator-inhibitor were absent or were smaller in patients who were given non-oral hormone therapy than those seen in trials of oral hormone therapy.

**Authors’ conclusions**

Potentially unfavourable effects on C-reactive protein and activated protein C were substantially smaller with non-oral hormone therapy than those seen with oral therapy. Non-oral hormone therapy had minor effects on other cardiovascular risk factors assessed. Compared with oral hormone therapy, non-oral therapy appeared safer with respect to atherosclerotic and venous thromboembolic disease risk.

**CRD commentary**

The review question and the inclusion criteria were clear. The authors searched some relevant databases. Some language restrictions were applied, which may have increased the chances of language bias. The authors did not report that they carried out a systematic search for unpublished studies, which may have increased the chances of publication bias. The authors reported that they used methods designed to reduce reviewer bias and error in the selection of studies, but not in the extraction of data. They did not report that they assessed the validity of included studies, which made the reliability of the evidence difficult to determine. Clinical heterogeneity between included studies and limited reporting of data meant the decision to employ a narrative synthesis was appropriate. The conclusions reflect the results of the review, but methodological and reporting shortcomings, and a lack of validity assessment in particular, make their reliability difficult to determine.

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

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that RCTs that used non-oral hormone therapy among early menopausal women were needed to establish the effects of non-oral hormone therapy on the incidence and mortality of atherosclerotic and venous thromboembolic disease.
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