Effects of continuous and cyclic hormone replacement therapy on the lipoprotein profile in postmenopausal women

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Authors' objectives
To provide an overview of the information concerning cyclic and continuous hormone replacement therapy (HRT), and the effects of the various regimens on the lipid profile.

Searching
MEDLINE was searched from January 1966 to December 1996, and Index Medicus from January 1995 to December 1996, for relevant studies and review articles. The bibliographies of selected articles were also reviewed.

Study selection
Study designs of evaluations included in the review
No inclusion criteria regarding study design were used. All included studies were randomised controlled trials and three were multicentre trials. The duration of follow-up ranged from 12 to 144 weeks.

Specific interventions included in the review
Cyclic and continuous oral HRT, consisting of a progesterone formulation along with conjugated equine oestrogen (CEE). Continuous therapy refers to the daily administration of oestrogen and a progestin, whereas cyclic therapy consists of progestin administered for 10 to 14 days each month along with daily oestrogen therapy. The continuous therapy regimens examined by the included studies were CEE (0.625 or 1.25 mg/day) plus medroxyprogesterone (MPA; 2.5, 5 or 10 mg/day), or CEE alone (0.625 mg/day). The cyclic regimens used by the included studies were:

CEE (0.625 mg/day) for 25 to 28 days plus MPA (10 mg) for 12 days;
CEE (0.625 mg/day) for 25 days plus MPA (10 mg) on days 12 to 25;
CEE (0.625 mg/day) for 25 to 28 days plus MPA (5 or 10 mg) on days 15 to 28;
CEE (0.625 or 1.25 mg/day) for 25 days plus MPA (10 mg) on days 16 to 25 days;
CEE (0.625 mg/day) for 25 days plus micronised progesterone (200 mg) for 12 days.

Two studies also included a placebo-treated group.

Participants included in the review
Postmenopausal women.

Outcomes assessed in the review
The lipid profile levels were measured with respect to low-density-lipoprotein cholesterol (LDL-C), high-density-lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The validity of the included studies was not formally assessed, although some aspects of methodological quality were discussed in the text (duration of follow-up and sample size) and presented in the summary table (randomisation and
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following data were extracted: reference details, number of participants, study design, duration of study, type of HRT (continuous or cyclic), dosing regimen used, and results (HDL-C, LDL-C, total cholesterol, and triglycerides).

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Nine randomised controlled trials involving 1,754 participants were included.

Six studies looked at the cyclic regimen using MPA (10 mg/day) for 10 to 14 days each month with CEE (0.625 mg/day) for 25 to 28 days. Five studies found a significant decrease in LDL-C compared with either baseline or placebo. Three studies looked at a cyclic regimen using a lower dose of MPA (5 mg/day) for 10 to 14 days per month with CEE (0.625 mg) on days 1 to 25. Both of these regimens were found to have negligible negative effects on the lipid profiles in these studies. The long-term effects on the lipid profile and endometrium remain unknown.

Three studies (20 to 60 participants) examined the use of CEE (0.625 mg/day) plus MPA (10 mg/day) for a duration of 12 to 24 weeks. The results of these studies showed that a higher dose of MPA given in continuous regimen is not advantageous for the lipid profile, because of its antagonistic oestrogen effects.

Five studies (60 to 875 participants) examined the use of lower doses of MPA (2.5 or 5 mg), administered in a continuous regimen with CEE (0.625 mg/day) for a duration of 12 to 144 weeks. The results showed significant increases in HDL-C levels and significant decreases in LDL-C levels.

Four studies compared continuous regimens with low-dose MPA and the traditional cyclic HRT regimen. The continuous HRT regimen, in comparison with the cyclic regimen, was not found to be detrimental to the lipid profile. Both regimens were found to be beneficial for increasing HDL-C and decreasing LDL-C levels.

The included studies reported variable triglyceride results. The two largest studies showed a significant increase in the triglyceride concentration in all treatment groups, regardless of the regimen involved.

Authors' conclusions
The lipid profile effects of HRT using continuous MPA were not significantly different from those obtained with cyclic MPA. The use of a continuous MPA regimen may also offer the long-term advantages of less vaginal bleeding and increased compliance.

CRD commentary
This was generally a poorly reported review and the results should be interpreted with caution. The aims of the review were clearly stated, but the inclusion criteria for the intervention and outcome measures were very broad and there were no inclusion criteria reported for the study design. Only two databases were searched, which means that some important information might have been missed. No attempt was made to look for unpublished data and the possibility of publication bias cannot be ruled out.
The methods used to select the studies for inclusion and to extract the data were not reported, and neither were the numbers of reviewers involved in these processes. The validity of the included studies was not formally assessed, although some aspects of validity were presented in the summary table and mentioned briefly in the text. Summary effect sizes (and a measure of their precision) were not presented for the included studies; it was only reported if the findings of the individual studies were significant or not, with the p-value reported for significant outcomes only. Where the authors discussed, in the text, the number of studies that found significant findings, it was generally not reported what the comparator had been.

The authors' conclusions do not appear to follow from the results of the review. The aim of the review was to look at the effects of continuous and cyclic HRT in terms of the lipid profile of postmenopausal women. However, the authors noted that eight of the included studies addressed the issue of breakthrough bleeding, endometrial hyperplasia, endometrial cancer, breast cancer and compliance. The findings, in terms of these outcomes, were reported for only one of these studies, on which the authors based part of their conclusions.

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

**Practice:** The authors state that a baseline triglyceride concentration and a total lipid profile should be obtained before initiation of HRT. If a patient has a triglyceride concentration of at least 500 mg/dL at baseline, the risks and benefits of initiating oral HRT must be considered carefully.

**Research:** The authors state that long-term, well-controlled studies examining the cardioprotective effects of oestrogen in addition to progestin for HRT are lacking.

**Bibliographic details**


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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.