Effects of hormone replacement therapy on the endometrium and lipid parameters: a review of randomized clinical trials, 1985 to 1995

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Authors' objectives
To determine the effects of hormone replacement therapy (HRT) on the endometrium and on lipid parameters.

Searching
MEDLINE was searched, and library searches of English language publications dating from January 1 1985 to January 31 1995 were performed. The medical subject headings used included 'hormone replacement therapy', '(o)estrogen', 'progestin' and 'postmenstrual'. Only published studies were included.

Study selection
Study designs of evaluations included in the review
Prospective, randomised clinical trials containing at least one HRT group.

For the endometrium parameters, each study included at least one HRT regime and 6 studies included at least one non-hysterectomised patient group receiving unopposed oestrogen therapy.

The duration of treatment, during which the effects of HRT on both outcomes (endometrium and lipid parameters) were evaluated, ranged from 3 to 36 months.

Specific interventions included in the review
HRT comprising oestrogen plus progestin, or oestrogen alone. The studies varied in the drug type given, the daily hormone doses, and the number of days within each cycle that the treatment was administered.

Participants included in the review
Details of the participants' characteristics were scarce.

Most of the lipid studies involved postmenopausal women who reached menopause naturally or surgically at least 6 months before therapy, and who were seeking relief of menopausal symptoms.

Outcomes assessed in the review
Endometrium and lipid parameters were assessed.

The primary endometrial outcome was endometrial hyperplasia.

All lipid analyses were performed on blood taken after fasting. When sequential therapy was evaluated, blood was drawn during the progestin phase of the cycle. The primary lipid outcomes were high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglyceride levels.

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 authors performed the selection.

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

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

**Methods of synthesis**

*How were the studies combined?*

The studies were combined narratively.

*How were differences between studies investigated?*

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

**Results of the review**

Forty-eight studies were included in the analysis. Eighteen studies (2,765 participants) focused on endometrial data, whilst 35 studies (3,085 participants) focused on lipid data (5 of these overlapped with studies focusing on endometrial data).

**Endometrial data.**

Unopposed oestrogen replacement therapy increased the incidence of endometrial hyperplasia, whilst the addition of progestin (in sufficient dose and duration) significantly reduced this risk.

In 6 studies that included at least one non-hysterectomised, unopposed oestrogen group, the incidence of hyperplasia increased with the duration of oestrogen treatment. The incidence of hyperplasia in these groups ranged from 'no change from baseline' to 62%.

In 5 of the 18 studies, hyperplasia developed in HRT-treated women, with the incidence ranging from 0.5 to 4.4% per study. It was not possible to determine from these studies whether the progestin type influences endometrial status.

**Lipid data.**

The hormone combinations produced a significant decrease in the serum total cholesterol and LDL cholesterol concentrations in the majority of the 35 studies (22 and 27, respectively), compared with baseline, placebo or reference values. In the remainder of the studies, the hormone combinations used had no significant effect on the serum total cholesterol and LDL concentrations. Unopposed oestrogen therapy produced similar results. In women who did not receive therapy, in 7 of the 13 studies that included a placebo or a reference group, the LDL cholesterol levels showed a non-signal increase.

The HDL cholesterol levels decreased in 9 of the 13 placebo or reference groups, and increased in all 8 unopposed oestrogen groups. Unopposed oestrogen therapy tended to increase triglyceride levels (7 of the 8 studies), whilst the oral replacement therapy regimens (oestrogen plus progestin) produced varying degrees of triglyceride increases over baseline, placebo or reference values, in the majority of the studies. Triglyceride concentrations, however, tended to decrease in most woman who received transdermal estradiol plus cyclic (dl)-norgestrel. The triglyceride levels varied among the 13 placebo or reference groups in all studies, ranging from -15% to +9% over baseline at 9 and 24 months, respectively.

Twelve studies indicated that medroxyprogesterone acetate (5.0 mg consistently or cyclically), when added to a daily dosage of conjugated oestrogens (0.625 mg/day), consistently resulted in increases of HDL cholesterol.

The two longest studies provided some insight into the treatment duration required for HRT (oestrogen plus progestin) to produce a significant effect on the lipid profile. In both studies the total cholesterol concentrations declined with the initiation of the treatment, largely because of LDL cholesterol reductions. The total cholesterol and LDL cholesterol were lowest after 6 months of therapy, and remained significantly less than the placebo or reference women for the duration of both studies.
Authors' conclusions
This review provides clear confirmation that the addition of progestin, in appropriate doses, to continuous oestrogen therapy provides protection against endometrial hyperplasia and the potential for endometrial carcinoma. The addition of non-androgenic progestins, in appropriate continuous or cyclic doses, to a continuous oestrogen regimen, also results in a more favourable lipoprotein profile than that seen in the women at baseline or in untreated postmenopausal women.

CRD commentary
The authors presented a well-defined review question. The inclusion and exclusion criteria were appropriate. The studies were summarised appropriately.

The search was very narrow and could have been extended to include other databases, such as EMBASE, and an attempt to identify unpublished literature. Publication bias cannot be ruled out. Some details of the primary studies were included, but more details of the participants' characteristics would have been useful. No validity assessment of the included studies was performed.

The authors' conclusions appear to follow from the results.

Implications of the review for practice and research
The authors did not state any implications for practice or further research.

Funding
Wyeth-Ayerst Research.

Bibliographic details

PubMedID
9609589

Indexing Status
Subject indexing assigned by NLM

MeSH
Endometrial Hyperplasia /chemically induced; Endometrial Neoplasms /chemically induced; Estrogen Replacement Therapy /adverse effects; Estrogens /administration & dosage; Female; Humans; Hyperlipidemias /chemically induced; Lipids /blood; Progestins /administration & dosage; Randomized Controlled Trials as Topic

AccessionNumber
11998000991

Date bibliographic record published
30/11/1999

Date abstract record published
30/11/1999

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.