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## EVIDENCE CENTRE LITERATURE SEARCH AND CRITICAL APPRAISAL

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**The bleeding patterns which can occur with long term Hormone  
Replacement Therapy (HRT) and how they correlate with  
endometrial pathology**

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*Southern Health Care Network*



## **SUMMARY STATEMENT:**

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## **REQUEST:**

The bleeding patterns which can occur with long term hormone replacement therapy (HRT) and how they correlate with endometrial pathology.

## **REQUESTED BY:**

**Dr Kylie McLachlan**, Endocrine Registrar, Menopause Clinic, Monash Medical Centre, Clayton.

## **METHODOLOGY**

### **Search Strategy**

The Centre for Clinical Effectiveness defined the ‘best available evidence’ as that research we can identify that is least susceptible to bias. We determine this according to pre-defined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomized controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalizable, or have other methodologic difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

## Details of Evidence Request:

Patient:	Menopausal women
Intervention:	Long term hormone replacement therapy (Cyclical, combined)
Comparison:	Menopausal women not on HRT (or short-term therapy)
Outcome:	Endometrial thickness, Endometrial pathology, uterine pathology, bleeding pattern.

### Search terms

Mesh: Hormone replacement therapy, oestrogen, estrogen, oestrogen replacement therapy.

Text word: HRT, estrogen.

### Resources Searched

- Cochrane Library CD-ROM

### Refinements, Searching & Reporting Constraints:

Our electronic searching of the above database was performed on 24 July 2000. No restriction was applied in our search strategy.

## RESULTS:

From the Cochrane database, two articles were identified (systematic review and meta-analysis). They were:

- ◆ Lethaby A, Farquhar C, Sarkis A, Roberts H, Jepson R, Barlow D. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding (Cochrane Review). In: The Cochrane Library, Issue 2, 2000. Oxford: Update Software (Complete review).
- ◆ Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone Replacement therapy and endometrial cancer risk: a meta-analysis. *Obstetrics & Gynecology*. 1995, 85(2), pp. 304-313.

A critical appraisal was conducted on the complete systematic review, but not on the meta-analysis. We are reasonably confident that the above articles represent the most important findings published to date based on our refinements, searching and reporting constraints.

## EVIDENCE SUMMARIES

### Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

# APPENDIX

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## Levels Of Evidence

As Defined By "A Guide To The Development, Implementation And Evaluation Of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 1998):

Level I		Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one properly designed randomised controlled trials.
Level III	-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series (either post-test or pre-test and post-test), opinions of respected authorities (narrative reviews), descriptive studies, reports of expert (i.e. consensus) committees, case studies.

<p><b>Evidence Summary Therapy</b></p> <p>The bleeding patterns which can occur with long term HRT and how they correlate with endometrial pathology</p>	<p>Lethaby A, Farquhar C, Sarkis A, Roberts H, Jepson R, Barlow D. Hormone replacement therapy in postmenopausal women: endometrial hyperplasia and irregular bleeding (Cochrane Review). In: The Cochrane Library, Issue 2, 2000. Oxford: Update Software. A substantive amendment to this systematic review was last made on 24 February 1999.</p>
<p><b>STUDY DESIGN &amp; NHMRC LEVELS OF EVIDENCE</b></p>	<p><b>Level I (Systematic review)</b></p>
<p><b>DESCRIPTION:</b> Subjects, Interventions, Comparisons, Outcomes, Exclusion Criteria</p>	<p><b>Patients:</b> Postmenopausal women with an intact uterus recruited from health care setting or through advertisements  <b>Intervention:</b> (administered for 6 to 36 months)</p> <ul style="list-style-type: none"> <li>◆ Oestrogen versus placebo</li> <li>◆ Oestrogen versus combined oestrogen/progestogen, either sequential (cyclic) or continuous</li> <li>◆ Combined oestrogen/progestogen (sequential or continuous) versus placebo</li> <li>◆ Combined oestrogen/progestogen (continuous) versus oestrogen/progestogen (sequential)</li> <li>◆ Sequential oestrogen/progestogen (progestogen once a month) versus sequential oestrogen/progestogen (progestogen once every 3 months).</li> </ul> <p><b>Comparison:</b> (see above)  <b>Outcomes:</b></p> <ul style="list-style-type: none"> <li>◆ Frequency of any type of endometrial hyperplasia or carcinoma</li> <li>◆ Irregular bleeding patterns (irregular bleeding and/or spotting or number of cycles with irregular bleeding/spotting)</li> <li>◆ Requirements for other therapy [endometrial biopsies, dilatation and curettage (D &amp; C)]</li> <li>◆ Adherence/compliance to therapy</li> </ul> <p><b>Exclusion Criteria:</b> Perimenopausal women (menstruation less than 6 months prior to study), intercurrent major disease, previous HRT (hormone replacement therapy) within one month of commencement of the study, any contraindication to HRT.</p>
<p><b>VALIDITY:</b> Methodology, rigour, selection, opportunity for bias</p>	<p><b>Search strategy:</b> Published and unpublished trials. Trials Register of the Cochrane Menstrual Disorders and Subfertility Group, MEDLINE, Embase, Current Contents, Biological Abstracts, Social Sciences Index, PsychLIT and CINAHL. The search strategy was developed by the Cochrane Menstrual Disorders and Subfertility Group.  <b>Randomisation:</b> The 18 studies reviewed were all RCTs. However, according to the reviewers:</p> <ul style="list-style-type: none"> <li>◆ In 9 of the trials the randomisation method was not given in detail.</li> <li>◆ Unclear allocation concealment in 10 trials.</li> <li>◆ Six of the 18 trials were not double blinded</li> </ul> <p><b>Validity:</b> Trials assessed for quality (including sensitivity analysis, heterogeneity)  <b>Potential for bias:</b> Some of the interventions were assessed based on data from one or two studies. As acknowledged by the reviewers, losses to follow up and withdrawals were common in the larger trials and trials with long duration.</p>
<p><b>RESULTS:</b> Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p><b>1) Oestrogen versus placebo</b></p> <ul style="list-style-type: none"> <li>◆ <b>Low dose:</b> Not significant</li> <li>◆ <b>Moderate dose:</b> Significant for endometrial hyperplasia at 6 months (OR=5.4, 95% CI 1.4-20.9), 12 months (OR=8.3, 95% CI 4.2-16.2), 24 months (OR=9.6, 95% CI 5.9-15.5) and 36 months (OR=16.0, 95% CI 9.3-27.5). Unscheduled biopsies or D &amp; C (OR=19.9, 95% CI 12.0-33.1, significant). Irregular bleeding after 6 months (OR=1.9, 95% CI 1.1-3.5, significant). Non adherence to therapy (OR=3.6, 95% CI 2.3-5.5, significant). Endometrial carcinoma (not significant).</li> </ul>

♦ **High dose:** The rate of endometrial hyperplasia was significant at 6 months (OR=9.1, 95% CI, 3.6-22.9), 12 months (OR=10.7, 95% CI 4.6-25.1) and 24 months (OR=13.1, 95% CI 5.9-29.0). Irregular bleeding after 6 months (OR=6.0, 95% CI 2.8-12.9, significant). Non adherence to oestrogen therapy (OR=6.8, 95% CI 3.4-14.0, significant). No cases of endometrial carcinoma reported in one small study that evaluated this outcome.

### 2) Oestrogen versus oestrogen and progestogen (continuous)

Endometrial hyperplasia under unopposed oestrogen treatment was significant at 6 months (OR=14.2, 95% CI 6.4-31.7), at 12 months (OR=15.0, 95% CI 9.7-23.2), at 24 months (OR=14.5, 95% CI 8.5-24.8) and at 36 months (OR=17.1, 95% CI 9.9-29.4). Unscheduled biopsies or D & C under unopposed oestrogen (OR=20.8, 95% CI 12.5-34.5, significant). Cycles of irregular bleeding or spotting during the 12 months of unopposed oestrogen was not significant (OR=0.8, 95% CI 0.73-0.9 and OR=0.6, 95% CI 0.56-0.7). Adherence to O+P than the unopposed oestrogen (OR=6.0, 95% CI 3.6-10.2, significant). Endometrial carcinoma rate not reported.

### 3) OESTROGEN VS OESTROGEN + PROGESTOGEN (sequential)

Endometrial hyperplasia under unopposed oestrogen was significant at 6 months (OR=11.6, 95% CI 5.5-24.5), 12 months (OR=15.2, 95% CI 10.0-22.9), 24 months (OR=19.8, 95% CI 11.1-35.6) and 36 months (OR=22.6, 95% CI 13.5-37.7). Unscheduled biopsies or D & C (OR=20.5, 95% CI 13.0-32.3, significant) and irregular bleeding under oestrogen treatment alone (OR=5.9, 95% CI 2.5-13.7 and OR=2.0, 95% CI 1.8-2.3, significant). Difference in adherence to therapy (OR=3.4, 95% CI 2.2-5.1, significant). No difference in the number of cycles of irregular bleeding. No cases of endometrial carcinoma.

### 4) OESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Difference in rates of endometrial hyperplasia or carcinoma, unscheduled biopsies or D & C and adherence to therapy (not significant). Irregular bleeding within 6 months of starting treatment and at longer durations under combined oestrogen-progestogen therapy was significant (OR=6.4, 95% CI 2.7-15.1) and (OR=6.1, 95% CI 2.7-13.7) respectively).

### 5) OESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

No difference in hyperplasia rates at 12 and 36 months but more likely under sequential therapy after 24 months (OR=4, 95% CI 1.2-14.0, significant). Endometrial cancer or irregular bleeding rates (not significant). Adherence to treatment in the placebo group (OR=3.5, 95% CI 1.5-8.1, significant).

### 6) OESTROGEN + PROGESTOGEN (continuous) VS OESTROGEN + PROGESTOGEN (sequential)

The rates of endometrial hyperplasia between the 2 types of combined treatment at 6, 12 and 24 months were not different. At 36 months, the frequency of hyperplasia was significantly lower under sequential treatment (OR=0.3, 95% CI 0.09-0.97). No significant differences in the rates of carcinoma, adherence to therapy, and irregular bleeding within 6 months and after 6 months of treatment. In the large MSG trial, there were higher rates of cycles with irregular bleeding and spotting in the continuous O + P treatment group ((OR=2.3, 95% CI 2.1-2.5) and (OR=1.6, 95% CI 1.5-1.8) respectively).

### 7) OESTROGEN + PROGESTOGEN (sequential, 1 month cycle) VS OESTROGEN + PROGESTOGEN (sequential, 3 month cycle)

Endometrial hyperplasia rates were significantly increased in the long cycle treatment group after 12 and 36 months of treatment in one multi centre study in Scandinavia (OR=0.11, 95% CI 0.03-0.52 and OR=0.18, 95% CI 0.06-0.49 respectively). This finding was not found in one other multi centre after 24 months of treatment. No difference in adherence to therapy and endometrial cancer rates between groups.

<p><b>AUTHORS COMMENTS:</b> Risk/benefit, limitations</p>	<ul style="list-style-type: none"> <li>◆ "For many of the comparisons, the outcomes were recorded by only one or two trials and sensitivity analysis could not be performed. Where more trials were included, the exclusion of poorer quality trials usually did not alter the results markedly".</li> <li>◆ "There is strong and consistent evidence in this review that unopposed oestrogen therapy, at moderate and high doses, is associated with increased rates of endometrial hyperplasia, irregular bleeding and consequent non adherence to therapy. The addition of oral progestogens administered either cyclically or continuously is associated with reduced rates of hyperplasia and improved adherence to therapy. Irregular bleeding is less likely under sequential than continuous therapy but there is a suggestion that continuous therapy over long duration is more protective than sequential therapy in the prevention of endometrial hyperplasia. Hyperplasia is more likely when progestogen is given every three months in a sequential regimen compared to a monthly progestogen sequential regimen."</li> <li>◆ "The findings of this review are more applicable to recent postmenopausal women (within 5 years of the menopause) than older postmenopausal women."</li> </ul>
<p><b>REVIEWER'S COMMENTS:</b> Risk/benefit, methodology, conclusions</p>	<ul style="list-style-type: none"> <li>◆ To date this review is the strongest evidence available in the literature.</li> <li>◆ The reviewers used well-developed criteria for study inclusion. They have acknowledged the strengths, weaknesses and implications of their findings for practice and future research.</li> </ul>