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Editorial

Hormone therapy in postmenopausal women and risk of endometrial hyperplasia: A Cochrane review summary

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The aim of this Cochrane review was to identify the minimum dose(s) of progestogen required to be added to estrogen in combined hormone therapy (HT) so that the rate of endometrial hyperplasia is not increased compared to placebo [1]. The primary outcome was the frequency of any type of endometrial hyperplasia or adenocarcinoma assessed by endometrial biopsy. Secondary outcomes were requirements for other medical or surgical therapy, adherence to therapy and withdrawal due to adverse events.

The protocol was amended from the original review, which considered bleeding patterns, as long term endometrial safety outcomes were considered to be clinically more important. Oral therapy only was considered, administered over a minimum period of 12 months. Included studies were those where endometrial assessment was planned for every participant at the end of the intervention. Endometrial assessment was either an endometrial biopsy for all women or measurement of endometrial thickness by transvaginal ultrasound, followed by endometrial biopsy in those women whose endometrial thickness was 5 mm or greater.

The main analyses were based on 46 trials that involved a total of 39,409 participants, although not all participants contributed to every outcome. The included participants were postmenopausal women with a uterus who had undergone a natural menopause or who had a bilateral oophorectomy. The term postmenopausal was defined as a serum FSH of 40 IU/L or greater or no menstruation for more than six months. Although STRAW criteria for postmenopausal is one year from the last menstrual period [2], the liberal interpretation was accepted as it was used in the majority of trials. Trials included the various comparisons and in order to make meaningful comparisons estrogens were grouped into low, moderate and high doses according to the advice of experts (Table 1)

1. Unopposed estrogen therapy vs placebo

There was both a dose–response and a duration of treatment–response relationship between unopposed estrogen and risk of hyperplasia. After one year of treatment, low-dose unopposed estrogen was associated with a marginally non-significant increase in endometrial hyperplasia compared to placebo. There was a significantly increased risk of endometrial hyperplasia at two and three years at all doses (moderate dose OR 11.86; high dose OR 13.06). There was no difference in the rate of early withdrawal due to adverse events between the low-dose or medium dose unopposed estrogen and placebo groups but withdrawal was significantly higher in the high-dose unopposed estrogen compared to placebo. Vaginal bleeding and endometrial hyperplasia were the main reasons given for discontinuation in the high-dose group.

2. Estrogen and progestogen vs placebo

There was no evidence of a statistically significant difference between continuous HT or sequential HT and placebo for endometrial hyperplasia or cancer after two to three years of therapy, nor for unscheduled biopsies or withdrawals owing to adverse events. All of the continuous regimens and the majority of sequential regimens showed no evidence of a difference in adherence to therapy. Withdrawal for uterine bleeding was the commonest reason for the three sequential regimens that showed a difference.

3. Estrogen and progestogen vs unopposed estrogen

In women with a uterus the addition of progestogen to unopposed estrogen therapy significantly reduced the risk of endometrial hyperplasia, with both sequential or continuous combined regimens (OR 13, 17 after three years). The progestogen in sequential therapy needed to be given for at least 10 days (Table 2).

Studies reporting the outcome of endometrial cancer showed no evidence of a difference in odds of developing endometrial cancer between women receiving unopposed estrogen and those receiving sequential or continuous combined regimens. However these women were closely monitored throughout the trial and if a diagnosis of endometrial hyperplasia was made, study treatment was stopped and appropriate treatment was provided. In addition an

Table 1
Estrogen doses (mg/day).

Estrogen	Low dose	Medium dose	High dose
Conjugated equine estrogen	≤0.45	0.625	1.25
Piperazine estrone sulphate	≤0.625	1.25, 1.5	2.5
Ethinyl estradiol	<0.01	0.01	>0.01
17 β Estradiol	≤1	1.5, 2	4
Estradiol valerate	0.5	1	2
Esterified estrogens	0.3	0.625	1.25

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Table 2
Minimum safe dose progestogen (days) for various types and doses of estrogen compared to placebo.

Estrogen	Combined continuous	Sequential
Low dose		
≤0.45 mg conjugated equine estrogen	1.5 mg medroxyprogesterone acetate	
1 mg 17 β estradiol	1 mg drosperinone 25 μg gestodene	5 mg dydrogesterone (14) 25 μg gestodene (12)
Moderate dose		
0.625 mg conjugated equine estrogen	2.5 mg medroxyprogesterone acetate	200 mg progesterone (12)
1.5 mg 17 β estradiol		150 μg desogestrel (14)
2 mg 17 β estradiol		1 mg norethisterone acetate (10) 10 mg dydrogesterone (14) 25 μg gestodene (12)
High dose		
2 mg estradiol valerate		10 mg medroxyprogesterone acetate (10)

adequate assessment of this risk was unlikely due to the limited follow up time frame for the trials in the review (maximum six years).

Only one RCT compared unopposed estrogen with combined regimens and reported adherence to therapy [3]. Adherence was greater in both continuous and sequentially combined regimens than in unopposed estrogen regimens. Withdrawals owing to adverse events and unscheduled biopsies were more likely in women receiving unopposed estrogen than in those receiving either continuous or sequential combined therapy. Unscheduled biopsies are more likely to be performed where there is concern about endometrial stimulation and consequent hyperplasia.

4. Continuous vs sequential regimens

In the trials that compared these regimens directly there was no evidence of a statistically significant difference in the odds of endometrial hyperplasia after one, two or three years nor in endometrial cancer after up to three years. However, the sequential regimens included in these comparisons were quite varied and there were insufficient data to determine the relative merits of the different types of regimens used. There was no evidence of a difference with regard to the outcome of adherence, withdrawal owing to adverse events or in the rate of unscheduled biopsies between the continuous and sequential regimens.

5. Continuous regimens

The comparisons between the various continuous combined regimens found no evidence of a statistically significant differences with regard to endometrial hyperplasia because all the regimens included in these comparisons were associated with very low rates of hyperplasia. There were no cases of endometrial cancer in the two studies that reported this outcome but the follow-up period in each was only one year.

6. Sequential regimens

The only sequential regimen that found a difference was a long cycle regimen. Long cycle sequential therapy (progestogen given once every three months) was compared with short-cycle sequential therapy (progestogen given once a month). In the largest trial where the long-cycle group received 2 mg 17 β estradiol daily + 1 mg norethisterone acetate for 10 days every three months, the rate of endometrial hyperplasia was so unexpectedly high in the first year (7.5%) that the trial was stopped early (mean duration of long-cycle therapy 2.8 years compared with the planned five years). The other smaller trials did not find any statistically significant difference between long-cycle and short-cycle groups in the rate of endometrial hyperplasia after one or two years but power calculations were not specified and one author commented that the study probably lacked power to find a difference between the groups.

7. Implications for practice and future reviews

The risk of hyperplasia, with the potential for progression to endometrial cancer, is increased for women using estrogen only therapy. Best practice in prescribing HT is to use both estrogen and progestogen in women with a uterus. The finding that low-dose unopposed estrogen was associated with an increase in the risk of endometrial hyperplasia over placebo at one year's duration that bordered on statistical significance needs to be confirmed by larger studies. There are various reasons for using the lowest dose of hormones for symptom relief. Women may need to take HT for some time as the median duration of symptoms is now thought to be four years [4]. As the addition of progestogen to estrogen appears to be responsible for the increased breast cancer risk use of the lowest possible dose may be a clinical imperative. Low-dose HT gives adequate relief of symptoms [5], however not all countries have generally available packaged oral low-dose sequential and combined continuous regimens. In this situation this review will help clinicians to separately prescribe low dose oral estrogen along with a progestogen dose that gives evidence based endometrial protection (Table 2). A review of transdermal delivery of hormones and intrauterine progestogen is needed.

Contributors

Helen Roberts wrote the initial draft of this editorial and was an author of the Cochrane review. Anne Lethaby commented on the initial draft and was an author of the Cochrane review. Martha Hickey commented on the initial draft and made substantial contributions to the 2008 update of the Cochrane review.

Competing interest

Helen Roberts is involved in research with Merck. None of this work is directly relevant to this paper.

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