Hormone therapy in postmenopausal women and risk of endometrial hyperplasia (Review)

Furness S, Roberts H, Marjoribanks J, Lethaby A, Hickey M, Farquhar C

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[Intervention Review]

Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Susan Furness[1], Helen Roberts[2], Jane Marjoribanks[3], Anne Lethaby[4], Martha Hickey[5], Cindy Farquhar[6]

[1]Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Manchester, UK. [2]Obstetrics & Gynaecology, Faculty of Medicine and Health Sciences University of Auckland, Auckland, New Zealand. [3]Obstetrics and Gynaecology, Cochrane Menstrual Disorders and Subfertility Group, Auckland, New Zealand. [4]Section of Epidemiology & Biostatistics, School of Population Health,University of Auckland, Auckland, New Zealand. [5]The University of Melbourne, The Royal Women's Hospital, Melbourne, Australia. [6]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand

Contact address: Susan Furness, Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Coupland III Bldg, Oxford Rd, Manchester, M13 9PL, UK. Susan.Furness@manchester.ac.uk. suefurness@gmail.com.

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ABSTRACT

Background

Declining circulating estrogen levels around the time of the menopause can induce unacceptable symptoms that affect the health and well being of women. Hormone therapy (both unopposed estrogen and estrogen/progestogen combinations) is an effective treatment for these symptoms, but is associated with risk of harms. Guidelines recommend that hormone therapy be given at the lowest effective dose and treatment should be reviewed regularly. The aim of this review is to identify the minimum dose(s) of progestogen required to be added to estrogen so that the rate of endometrial hyperplasia is not increased compared to placebo.

Objectives

The objective of this review is to assess which hormone therapy regimens provide effective protection against the development of endometrial hyperplasia and/or carcinoma.

Search strategy

We searched the Cochrane Menstrual Disorders and Subfertility Group trials register (searched January 2008), *The Cochrane Library* (Issue 1, 2008), MEDLINE (1966 to May 2008), EMBASE (1980 to May 2008), Current Contents (1993 to May 2008), Biological Abstracts (1969 to 2008), Social Sciences Index (1980 to May 2008), PsycINFO (1972 to May 2008) and CINAHL (1982 to May 2008). Attempts were made to identify trials from citation lists of reviews and studies retrieved, and drug companies were contacted for unpublished data.

Selection criteria

Randomised comparisons of unopposed estrogen therapy, combined continuous estrogen-progestogen therapy and/or sequential estrogen-progestogen therapy with each other or placebo, administered over a minimum period of twelve months. Incidence of endometrial hyperplasia/carcinoma assessed by a biopsy at the end of treatment was a required outcome. Data on adherence to therapy, rates of additional interventions, and withdrawals due to adverse events were also extracted.

Data collection and analysis

In this substantive update, forty five studies were included. Odds ratios were calculated for dichotomous outcomes. The small numbers of studies in each comparison and the clinical heterogeneity precluded meta analysis for many outcomes.

Main results

Unopposed estrogen is associated with increased risk of endometrial hyperplasia at all doses, and durations of therapy between one and three years. For women with a uterus the risk of endometrial hyperplasia with hormone therapy comprising low dose estrogen continuously combined with a minimum of 1 mg norethisterone acetate or 1.5 mg medroxyprogesterone acetate is not significantly different from placebo (1mg NETA: OR=0.04 (0 to 2.8); 1.5mg MPA: no hyperplasia events).

Authors' conclusions

Hormone therapy for postmenopausal women with an intact uterus should comprise both estrogen and progestogen to reduce the risk of endometrial hyperplasia.

PLAIN LANGUAGE SUMMARY

Hormone therapy for postmenopausal women with intact uterus

Hormone therapy may be used to manage troublesome menopausal symptoms, but is currently recommended to be given at the lowest effective dose and regularly reviewed by a woman and her doctor. In women with an intact uterus hormone therapy comprising estrogen and progestogen is desirable to minimise the risk of endometrial hyperplasia which can develop into endometrial cancer. Low dose estrogen plus progestogen (minimum of 1 mg norethisterone acetate or 1.5 mg medroxyprogesterone acetate) taken daily (continuously) appears safe for the endometrium. For women within one year of menopause low dose estrogen combined sequentially with 10 days of progestogen (1mg norethisterone acetate) per month appears safe for the endometrium.

BACKGROUND

Description of the condition

Menopause means the cessation of menstruation and typically occurs in women aged between 45 and 55 years with a mean age of about 51 years. Women are said to be postmenopausal when menstruation has ceased for 6 to 12 months and blood serum levels of follicle stimulating hormone (FSH) increase to at least 49 IU/L. The decline in circulating estrogen around the time of the menopause can induce symptoms that affect the well being and health of women; hot flushes, insomnia, declining bone mass, night sweats, mood disturbances and vaginal dryness have all been reported. As life expectancy and the proportion of older adults in the population increases, there has been an increased focus on the effects of ageing. Estrogen therapy has been utilised for the treatment of many of the menopausal symptoms, particularly hot flushes and vaginal dryness.

Description of the intervention

Hormone therapy may consist of either unopposed estrogen or a combination of estrogen and progestogen.

Unopposed estrogens include conjugated equine estrogen (CEE), ethinyl estradiol (EE), micronized 17B-estradiol (E2), estradiol valerate (EV), estrone sulphate (EIS) and esterified estrogens (ESE). These estrogens cannot be considered equal. They vary in their dose equivalency and have different metabolic effects on different tissues or end organs. In order to make meaningful comparisons estrogens were grouped into low moderate and high doses according to the advice of experts (France 1998; MacLennan 1998; Ansbacher 1994; O'Connell 1998).

There are a number of different progestogens used in hormone therapy, which can be classified according to their structure and/or bioactivity (Maitra 2004). These include

- micronized progesterone (MP), dydrogesterone (a retroprogesterone), and progesterone derivatives such as medrogestone (MG).
- pregnanes such as medroxyprogesterone acetate (MPA),

megestrol acetate (MA), cyproterone acetate (CPA),

- nor pregnanes such as trimegestone (TMG), nestorone and promegestone.
- estranges such as norethisterone, norethisterone acetate (NETA) and lynestrol, derived from testosterone and collectively known as first generation progestogens.
- gonane progestogens which can be divided into 2 categories - the second-generation progestogens such as norgestrel, levonorgestrel (LNG) and the third generation progestogens such as desogestrel (DG), gestodene, norgestimate (NGM) and dienogest.
- drospirinone - a new progestogen derived from spironolactone not included in the generation classification.

Some progestogens are prodrugs which are metabolised by the liver into active compounds. Examples are promegestone which is converted to trimegestone, and norgestimate which is converted to norgestrel.

Why it is important to do this review

Several studies have suggested a causal relationship between unopposed estrogen therapy (daily use of estrogen without the addition of progestogen) and the induction of endometrial hyperplasia and carcinoma (Ziel 1975; Smith 1977; Gardan 1977; Antunes 1979; Grady 1995; HOPE 2001). Endometrial hyperplasia is regarded as a precursor of endometrial cancer but progression is dependent on the type of hyperplasia (Terakawa 1997; Kurman 2000). The estimated risk of hyperplasia progression to cancer is 1%, 3%, 8% and 29% for women with simple, complex, simple atypical, and complex atypical hyperplasia, respectively (Kurman 1985). The risk of hyperplasia and/or carcinoma appears to increase with higher doses and increased duration of unopposed estrogen treatment (Speroff 2005). Adding a progestogen to estrogen therapy significantly reduces the risk of hyperplasia (Whitehead 1977; Cust 1990, Udoff 1995; Corson 1999), but can result in premenstrual symptoms which are problematic for some women. These symptoms and increased bleeding and spotting with both types of HT regimen are often given as a reason not to continue hormone therapy (Ellerington 1992; Rozenberg 2001). An additional concern is that the addition of progestogen to estrogen also appears to increase the risk of cardiovascular disease and breast cancer (WHI 2002).

As a result of evidence suggesting that hormone therapy is associated with an increased risk of cardiovascular disease and breast cancer in women aged over 55 years (WHI 2002), current advice is that hormone therapy not be used for chronic disease prevention. Hormone therapy is an effective treatment for women with menopausal symptoms of hot flushes, night sweats and vaginal dryness and the duration of therapy should be decided for individual women based on an assessment of both benefits, in terms of menopausal symptom management and harms of therapy, such as venous thromboembolism (Hickey 2005; Roberts 2007). The duration of treatment with hormone therapy should be reviewed by a woman with her doctor, because for most women hot flushes resolve within a year of onset of the menopause. About one third of women will continue to have vasomotor symptoms for up to 5 years and some women for even longer (Hickey 2005).

Hormone therapy is usually taken orally, but there are also other modalities including transdermal (patches, gels and creams), subcutaneous (implants), intranasal, vaginal and intrauterine. This review will consider only oral hormone therapy and the other modalities will be covered in separate reviews.

The original version of this review investigated abnormal vaginal bleeding, and concluded as follows:

Regular withdrawal bleeding is expected with a sequential regimen of estrogen and progestogen (E + P) but women appear to experience less irregular bleeding than with a continuous E + P regimen. Irregular bleeding or spotting is common in the first year of continuous E + P but following the first year of treatment, bleeding and spotting become more common in sequential E + P regimens. A large proportion of women taking continuous E + P become amenorrhoeic after a year of therapy whilst withdrawal bleeding continues for women taking sequential regimens.

Whilst bleeding during the first year of continuous E + P therapy does not need investigation with vaginal ultrasound scan, endometrial thickness and/or endometrial biopsy, these investigations should be considered in the second and subsequent years of hormone therapy. Unscheduled bleeding on sequential HT should be investigated by hysteroscopy and endometrial biopsy.

For the 2008 update of this review, we will address long-term endometrial safety outcomes rather than bleeding patterns, and we have amended the protocol accordingly. We aim to assess which of the oral hormone therapy regimens, unopposed estrogen or estrogen-progestogen administered either continuously or sequentially, provides the best protection against the development of endometrial hyperplasia or carcinoma, has better adherence to therapy regimens and the lowest rate of unscheduled biopsies. In addition we aim to compare the effects of different types, doses and duration of progestogen use on both endometrial hyperplasia and adherence to treatment, in order to determine the minimum dose and duration of progestogen required for endometrial protection.

Amendments to the original protocol

For the 2008 update of this review, the protocol has been amended to include only studies with a minimum of 12 months of therapy with either unopposed estrogen, or combined estrogen and progestogen. The primary outcomes will be endometrial hyperplasia and/or carcinoma, with secondary outcomes of adherence to therapy, withdrawal due to adverse events and rate of unscheduled investigations for abnormal bleeding (hysteroscopy and endometrial biopsy). Bleeding patterns are no longer an outcome in this

updated review.

OBJECTIVES

To assess which oral hormone therapy regimens provide the most effective protection against the development of endometrial hyperplasia and/or carcinoma.

Information from the studies concerning the need for other medical or surgical therapy (such as unscheduled endometrial biopsies or hysteroscopy procedures), withdrawal due to adverse events, and adherence to therapy will also be included where the data are available.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials of oral estrogen (E) or oral combined estrogen/progestogen (E + P) therapy versus placebo, oral estrogen versus combined oral estrogen/progestogen (sequential or continuous therapy), oral estrogen/progestogen (continuous) versus oral estrogen/progestogen (sequential) with a minimum treatment period of twelve months.

Types of participants

Inclusion criteria

Postmenopausal women with an intact uterus, defined as women who have not menstruated for more than six months and who have a serum FSH greater than or equal to 40 IU/L. It is recognised that this criterion is relatively liberal and that a common definition of postmenopausal status requires a minimum of 12 months to elapse since last menses, but the majority of trials use this more liberal criterion and postmenopausal status is often further confirmed by FSH levels. The definition includes women who have undergone a natural menopause and women who have had bilateral oophorectomy (removal of both ovaries). The participants can be recruited from any health care setting or from advertisements.

The progestogens also vary in dose equivalency and metabolic effects on different tissues. As all progestogens share in common the effect of inducing a morphogenic change in estrogen-primed endometrium, the potency of a progestogen can be expressed by the difference in dose required in order to achieve this transformation. Estimates of potency based on animal studies give a "transformation dose" per cycle (Kumar 2000). However the serum level result-

Exclusion criteria

Perimenopausal women (menstruation less than six months prior to study)
Intercurrent major disease
Previous HT (hormone therapy) within one month of commencement of the study
Any contraindication to HT (either unopposed estrogen or estrogen + progestogen therapy)
Current use of other sex steroids including tibolone

Types of interventions

Oral interventions administered for a period of twelve months or greater.
(1) Unopposed estrogen versus placebo (low, moderate or high dose)
(2) Combined estrogen + progestogen (continuous) versus placebo
(3) Combined estrogen +progestogen (sequential) versus placebo
(4) Unopposed estrogen versus combined estrogen/progestogen (continuous)
(5) Unopposed estrogen versus combined estrogen/progestogen (sequential)
(6) Combined estrogen + progestogen (continuous) versus estrogen/progestogen (sequential)
(7) Continuous combined estrogen + progestogen (dose comparisons)
(8) Sequential combined estrogen + progestogen (dose/regimen comparisons)

Estrogens vary in their dose equivalency and have different metabolic effects on different tissues or end organs. In order to make meaningful comparisons, estrogens were grouped into 'low', 'moderate' and 'high' dose subgroups. The allocations of different types and doses of estrogens to these groupings were made according to the literature and the advice of experts (France 1998; MacLennan 1998; Ansbacher 1994; O'Connell 1998) and are set out in Table 1. Disagreement persists among clinical experts, however, regarding categorisation of 17β estradiol in the moderate range and two different doses (1.5mg and 2 mg) of this estrogen have sometimes been included in this category. From the information available (Ansbacher 1994) 0.010 mg ethinyl estradiol can be considered equivalent to 0.625 mg conjugated equine estrogens and can be considered a moderate dose. Consequently we have modified the categorisation of ethinyl estradiol doses in this update of the review.

ing from administration of progestogen to women is dependent on a number of variables including the mode of administration, absorption, metabolism, distribution and storage in fat and other tissues, binding to serum proteins, inactivation and conjugation. We were unable to find empirical evidence as to a "transformation dose" per cycle in women. In this review we attempted to order the progestogens based on estimates of their relative potency from animal studies (Kumar 2000) as there are few data from studies in humans as to dose equivalency of progestogens used in hormone therapy.

In the analysis, continuous and sequential E + P regimens were evaluated separately. For each type of regimen, different doses were compared.

There is evidence that progestogens must be taken for at least 10 days per month to reduce the risk of endometrial hyperplasia and carcinoma (Whitehead 1981) though some studies suggest that progestogens should be given for at least 12 to 14 days (Sturdee 1994; Whitehead 1987; Archer 2001). It was planned to assess separately the effects of sequential progestogen given for less than and more than 10 days per cycle.

The effects of sequential therapy were evaluated separately for different doses and duration of progestogen treatment, and for different treatment regimens (monthly sequential, long cycle (3 monthly sequential) and intermittent (3 days E only followed by 3 days E+P, repeated).

Types of outcome measures

Primary outcomes

(1) Frequency of endometrial hyperplasia (of any type) or adenocarcinoma (assessed by endometrial biopsy)

Secondary outcomes

(1) Requirements for other medical or surgical therapy (e.g.. unscheduled endometrial biopsies, hysteroscopy)
(2) Adherence/compliance to therapy
(3) Withdrawal due to adverse events

Included studies are those where endometrial assessment is planned for every participant at the end of the intervention. Endometrial assessment may be 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 is 5mm or greater. Studies which do not report rates of endometrial hyperplasia will be excluded.

In this review we have used the outcome *withdrawal due to adverse events* as a proxy for the acceptability of the therapy regimens to women. It is defined as withdrawal due to adverse events prior to the end of the planned therapy period whether or not the investigator considered that the event was related to the therapy.

Search methods for identification of studies

We searched for all publications which describe (or might describe) randomised controlled trials of:

- estrogen versus estrogen-progestogen or placebo
- estrogen-progestogen versus placebo
- combined continuous estrogen-progestogen versus sequential estrogen-progestogen therapy
- sequential combined estrogen and progestogen where different regimens are compared

and their impact on rates of endometrial hyperplasia or cancer in postmenopausal women.

Electronic searches

The original search was performed in 1998. Updated searches were completed in 2003, July 2007 and May 2008.

(1) We searched the Menstrual Disorders and Subfertility Group's trials register for any trials (searched January 2003 July 2007 and May 2008). See Review Group for more details on the make-up of the trial register. The following search strategy was used:
((Keywords = "*Menopaus*" or Keywords = "postmenopaus*" or #43= "menopaus*" or #43="postmenopausal")
AND
(Keywords ="*Hormone Therap*" or Keywords = "HRT*" or Keywords = "HT* ")
AND
(Keywords = "endometrial biops*" or Keywords ="endometrial hyperpla*" or Keywords ="endometrial response*" or Keywords = "endometrial proliferat*" or Keywords ="bleeding*" or #43= "bleeding pattern*"))
AND NOT
(Keywords = "tibolone" or Keywords = "SERM" or Keywords = "raloxifene" or Keywords = "phytoestrogen*")

(2) We searched *The Cochrane Library* (Issue 2, 2008), MEDLINE (1966 to May 2008), EMBASE (1980 to May 2008), Current Contents (1993 to May 2008), Biological Abstracts (1969 to 2008), Social Sciences Citation Index (1980 to May 2008), PsycINFO (1972 to May 2008) and CINAHL (1982 to May 2008).

These electronic databases were searched using the highly sensitive search strategy developed by the Cochrane Collaboration together with the following terms:

1. exp climacteric/ or exp menopause/
2. (climacter$ or menopaus$).tw.
3. (postmenopaus$ or post-menopaus$ or post menopaus$).tw.
4. or/1-3
5. exp estrogens/
6. exp Contraceptives, Oral, Combined/
7. hormone replacement therapy/ or estrogen replacement therapy/
8. exp Progestins/

9. (hormone replacement therapy or HRT).tw.
10. (estrogen$ or progest$).tw.
11. or/5-10
12. 4 and 11
13. endometrial hyperplasia/
14. (endometri$ adj5 hyperplasia).tw.
15. (endometri$ adj5 carcinoma).tw.
16. (endometri$ adj5 (biops$ or histology)).tw.
17. (hysteroscop$ or hysterectomy).tw.
18. (adherence or compliance).tw.
19. or/13-18
20.12 and 19

The output from these searches was transferred to a database, where duplicates were identified and removed. Abstracts were read to identify publications of trials that were eligible for inclusion. We obtained paper copies of all potentially eligible studies. Where there was insufficient information available electronically we obtained paper copies to establish whether a study met the inclusion criteria for this review.

Searching other resources

(1) We searched citation lists of included trials, conference abstracts and relevant review articles. Relevant journals were handsearched for additional trials (see Review Group details for more information) and drug companies were contacted for details of unpublished trials.

(2) We made attempts to contact the corresponding author of included trials where data were not in a form suitable for extraction or where information relating to the study was not explicit.

Data collection and analysis

Selection of studies

The selection of trials for inclusion in the review was performed by at least two reviewers working independently for each of the versions of this review, after employing the search strategy described previously. For the 2008 update of the review selection of included trials was undertaken independently by three reviewers (JM, SF & AL) with any discrepancies resolved by discussion.

Data extraction and management

Included trials were assessed independently by at least two of the reviewers for the following quality criteria and methodological details, with any discrepancies resolved by discussion:

Trial characteristics

(1) Method of randomisation
(2) Presence or absence of blinding to treatment allocation
(3) Quality of allocation concealment
(4) Number of women randomised, excluded or lost to follow up
(5) Whether an intention to treat analysis was done
(6) Whether a power calculation was done
(7) Duration, timing and location of the study

Characteristics of the study participants

(1) Age and any other recorded characteristics of women in the study
(2) Other inclusion criteria
(3) Exclusion criteria

Interventions used

(1) Doses and types of unopposed estrogen therapy used
(2) Doses, types and regimens of estrogen-progestogen therapy used
(3) Duration of hormone therapy

Outcomes reported

(1) Endometrial hyperplasia as assessed by endometrial biopsy
(2) Endometrial cancer as confirmed by histology
(3) Requirements for additional investigations to exclude endometrial pathology including ultrasound, endometrial biopsy or hysteroscopy, or saline infusion sonography.
(4) Adherence/compliance to therapy

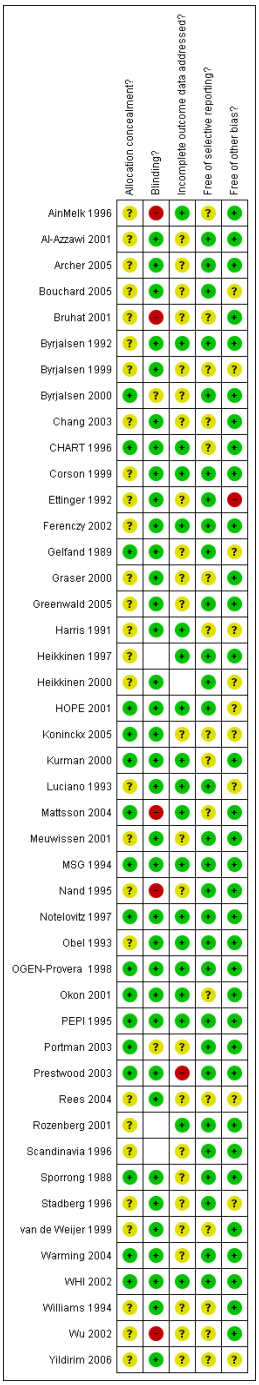
Data extraction and quality assessment were also performed independently by at least two reviewers, using forms designed according to Cochrane guidelines (Higgins 2008 Table 7.3), with any discrepancies resolved by discussion. Quality of allocation concealment was graded as either A (adequate), B (unclear) or C (inadequate). Reviewers included clinical experts and reviewers with statistical or methodological expertise. Where necessary, additional information on trial methodology or original trial data were sought from the corresponding author of any trials that appeared to meet the eligibility criteria.

For the 2008 update of this review study selection, data extraction and quality assessment was performed by AL, JM and SF.

Assessment of risk of bias in included studies

Risk of bias was assessed according to the method described by Higgins 2008 Figure 1.

Figure 1. Summary of risk of bias : review authors' judgments about each risk of bias domain for each included study (refer table of included studies/risk of bias section, for details)



In order to determine the likelihood of publication bias a funnel plot was planned.

Assessment of heterogeneity

Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points and the overlap in their confidence intervals and, more formally, by checking the Q statistic and I^2 quantity (Higgins 2002). As a rough rule of thumb, a value of I^2 of 25% or less can be considered a low degree of heterogeneity, a value around 50% moderate heterogeneity and a value of 75% or more high heterogeneity. A priori, it was planned to look at the possible contribution of differences in trial design to any heterogeneity identified in this manner.

Data synthesis

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group. Where it was clinically appropriate, study outcomes were pooled statistically. It was planned to use a fixed effect model for calculation of summary effects in the meta-analysis. Where significant heterogeneity was demonstrated it was planned to calculate summary effects using a random effects model to take account of the added uncertainty.
Comparisons were subgrouped according to the HT regimen (E only, E+P combined either continuously or sequentially) and also by estrogen dose (grouped as low, moderate or high dose - see table 2) and by progestogen type and dosage given.
For dichotomous data (for example, proportion of participants with hyperplasia or carcinoma), results for each study were expressed as an odds ratio with 95% confidence intervals and combined for meta-analysis with RevMan software using the Peto-modified Mantel-Haenszel method. All of the outcomes apart from adherence to therapy were categorised so that a high value represented a harm or negative consequence rather than a benefit of treatment. Thus, a negative consequence of treatment is in most cases represented in the graphs as a odds ratio and confidence interval on the right of the centre line.
In order to avoid double counting we chose to use subtotals only where there was a single reference group (e.g. unopposed estrogen or placebo) and two or more comparison groups in a trial.
Where possible we took an intention to treat approach and used the number of women randomised to each group to calculate the rates of hyperplasia. This approach is based on the assumption that women who stopped hormone therapy and did not return for a biopsy, did not have endometrial hyperplasia.

Sensitivity analysis

We also planned a priori sensitivity analyses comparing the pooled results of all trials with:
(i) Trials with adequate concealment (score A)
(ii) Trials with double blinding
(iii)Trials with < 20% withdrawals
where there were sufficient studies to make this possible.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Due to the changes in the protocol for the 2008 update, twelve previously included studies were excluded from this updated version of the review; three because they had less than 12 months of therapy (Blumel 1994, Pinto 2003, Von Holst 2002), and nine because the primary outcomes were bleeding patterns and these studies did not report endometrial hyperplasia as an outcome (Archer 1999, Hagen 1982, Limpaphayom 2000, Marslew 1991, Marslew 1992, Mizunuma 1997, Simon 2001, Simon 2003, Williams 1990). Three studies previously excluded because they are dose finding studies are now included (Bruhat 2001, Graser 2000, OGEN-Provera 1998). An additional 28 studies were identified that met the inclusion criteria, to give a total of 45 studies included in the updated review.

Included studies

The main analyses were based on 45 trials which involved a total of 38,702 participants randomised to treatment. Not all of the women randomised completed the total period of follow up or were included in an intention to treat analysis. Data extraction was independently performed by at least two authors (SF, JM, AL).
The trials took place in USA (15 trials: Archer 2005, CHART 1996, Corson 1999, Ettinger 1992, Greenwald 2005, Harris 1991, Kurman 2000, Luciano 1993, Notelovitz 1997, PEPI 1995, Portman 2003, Prestwood 2003, WHI 2002, Williams 1994, HOPE 2001), Denmark, Norway and Sweden (three studies: Mattsson 2004, Okon 2001, Scandinavia 1996), Denmark (five studies: Byrjalsen 1992, Byrjalsen 1999, Byrjalsen 2000, Obel 1993; Warming 2004), Finland (two trials; Heikkinen 1997, Heikkinen 2000), Sweden (two trials; Sporrong 1988, Stadberg 1996), The Netherlands (van de Weijer 1999), Europe

(Meuwissen 2001), Europe and Scandinavia (Rozenberg 2001), Europe, Scandinavia and the UK (Bouchard 2005), Europe and UK (Al-Azzawi 2001, Koninckx 2005, Rees 2004), Europe and South Africa (Graser 2000), France and Germany (Bruhat 2001) and Turkey (Yildirim 2006). One large trial took place in 99 centres in the USA and Europe (MSG 1994), one in Canada (AinMelk 1996) and two in both Canada and The Netherlands (Ferenczy 2002, Gelfand 1989). There was one included trial from China (Wu 2002), one from Taiwan (Chang 2003) and two from Australia (Nand 1995, OGEN-Provera 1998).

Participants

Most of the included trials specified that women be postmenopausal and this was defined in 32 trials as cessation of bleeding for six months or more prior to entry into the study. In two trials postmenopausal was defined as serum FSH >/= 40 IU/L (CHART 1996, Rozenberg 2001), in four trials postmenopausal was defined as serum FSH "in the postmenopausal range" (Harris 1991, Heikkinen 1997, Nand 1995, Warming 2004) and in one trial postmenopausal was defined as estradiol <20 pg/ml (Greenwald 2005). Seven studies did not define postmenopausal (Byrjalsen 1992, Byrjalsen 1999, Mattsson 2004, Scandinavia 1996, Stadberg 1996, Warming 2004, Wu 2002) and in one trial the inclusion criteria specified that participants be older than 65 years and consequently postmenopausal (Prestwood 2003).

Participants ranged in age from 40 to 75 years although in most studies women were in the early menopause with the requirement that women should be within five or less years of their last spontaneous menstrual bleeding. Results can thus be generalised only to women in the early postmenopause rather than all postmenopausal women. Most of the trials also required that women have an intact uterus, or this was implied by the requirement for an endometrial biopsy at baseline, exclusion criterion of previous gynaecological operation or the nature of the primary outcomes. Full details of the inclusion and exclusion criteria for each study are found in the Characteristics of included studies. Common exclusion criteria were malignancy, chronic illness, or use of contraindicated medications.

Interventions

A wide variety of unopposed estrogen or estrogen + progestogen combinations were used as interventions in the included trials. Unopposed estrogens included conjugated equine estrogens (CEE), estradiol valerate (EV), estrone sulphate (EIS), esterified estrogens (ESE), micronised 17B-estradiol (17βE2), oestrone sulphate(ES), and piperazine estrone sulphate (POS). Two studies (CHART 1996; Portman 2003) compared placebo with unopposed ethinyl estradiol at 4 different doses and with the same doses continuously combined with norethisterone acetate. Most of the unopposed estrogen studies compared different doses of the same drug with placebo.

A number of different progestogens were used in the studies included in this review. In alphabetical order these included cyproterone acetate (CPA), desogestrel, dienogest (DNG), drospirinone (DSP), dydrogesterone (DYG), gestodene, medroxyprogesterone acetate (MPA), megestrol acetate (MEGA), norgestrel (NG), norethisterone acetate (NETA), norgestimate (NGM), levonorgestrel (LNG) and trimegestone (TMG).

In some trials, unopposed estrogen treatment (E) was compared with estrogen/progestogen combined treatment (E + P), either continuous or sequential.

Sequential combined regimens of hormone therapy may be divided into four main types. The most common regimens use unopposed estrogen for part of the cycle followed by estrogen plus progestogen for 10 -15 days per monthly cycle (28 to 30 days). Alternatively there are experimental regimens that use intermittent progestogen ie estrogen only for 3 days followed by estrogen plus progestogen for 3 days repeated for up to a year (Byrjalsen 2000, Corson 1999, Rozenberg 2001). Some studies have used regimens where progestogen is added for 10 -12 days every two or three months (Heikkinen 1997;Scandinavia 1996;Williams 1994) or every 6 months (Prestwood 2003) (long cycle regimens). In one study (Rees 2004) a biphasic regimen comprising 11 days of unopposed estrogen and 10 days of E+P followed by 7 days of placebo, was compared with a triphasic regimen comprising 12 days of unopposed estrogen followed by 10 days of E+P, followed by 6 days of lower dose E only. The biphasic regimen in this study was similar to the cyclical regimens that were originally used in hormone therapy but were found to be unsatisfactory for women because the troublesome menopausal symptoms returned during the 7 day placebo phase.

In this review, duration of progestogen therapy varied from 10 to 14 days and it was given at differing times in the treatment cycle. Where there was only one comparison group of unopposed estrogen and two or more groups with different E + P doses (MSG 1994; PEPI 1995), we chose to use subtotals only, to avoid double counting the comparison group. Likewise, in evaluating the effects of combined E + P, both continuous and sequential, where there was only one comparison group the analyses use subtotals only.

Sixteen of the trials had a placebo control group. Five studies had an estrogen only group as the comparison with combined regimens (Archer 2005, Corson 1999, Gelfand 1989, MSG 1994, PEPI 1995). Eleven trials compared two or more different continuous combined regimens or dosages (AinMelk 1996, Bouchard 2005, Bruhat 2001, Graser 2000, Heikkinen 2000, Kurman 2000, Mattsson 2004, Nand 1995, OGEN-Provera 1998, Wu 2002, Yildirim 2006). Seven studies compared two or more sequential regimens or dosages (Chang 2003, Meuwissen 2001, Okon 2001, Rees 2004, Scandinavia 1996, van de Weijer 1999, Williams 1994), and a further six compared a combined sequential regimen with a combined continuous regimen (Al-Azzawi 2001, Koninckx 2005, Luciano 1993, Rozenberg 2001, Sporrong 1988, Stadberg 1996).

Duration of treatment in the included trials ranged from twelve months to six years but the majority of studies assessed treatment over either one or two years.

Outcomes

The primary outcomes were frequency of endometrial hyperplasia or carcinoma. Some studies assessed endometrial thickness by ultrasound and only performed a biopsy where endometrial thickness was greater than 5 mm. This would appear to be common clinical practice. Endometrial hyperplasia was invariably confirmed by endometrial biopsy and reported at 12, 24 and 36 months. Most studies included any type of hyperplasia as a hyperplasia outcome. A subgroup of women from the Women's HOPE study were followed up for 2 years and there were no additional cases of endometrial hyperplasia in the second year except in the women on unopposed estrogen. In another study (Rozenberg 2001) participants were initially randomised to treatment for one year and then an open label extension study followed for a second year. Only 65% of those women initially randomised had endometrial biopsies at the end of the second year.

Incidence of endometrial carcinoma was measured as an outcome by thirteen studies (Al-Azzawi 2001, Byrjalsen 1999, Chang 2003, Ferenczy 2002, Koninckx 2005, Kurman 2000, Meuwissen 2001, MSG 1994, Notelovitz 1997, Obel 1993, PEPI 1995, Scandinavia 1996, WHI 2002) at different time points after 1, 2, 3 or 5+ years of treatment.

A small number of trials (Ettinger 1992; Harris 1991; Notelovitz 1997; Heikkinen 1997; Rozenberg 2001) assessed change in bone density, lipid profile and/or climacteric symptoms as the primary outcomes. Effects on the endometrium and frequency of unscheduled bleeding were secondary outcomes.

The frequency of unscheduled biopsies or dilation and curettage was measured in one large trial (PEPI 1995), and non adherence to treatment as measured by pill counts was assessed in only 2 studies (PEPI 1995, Rees 2004). However there were significant numbers of participants in most of the trials who withdrew from the trial prior to completion (10-50%), either due to adverse events, lack of efficacy or other reasons.

Excluded studies

We retrieved paper copies of an additional forty eight studies identified as potentially eligible for inclusion. These were evaluated and subsequently excluded. Twenty four studies had primary outcomes of bleeding patterns or bone mineral density and did not include planned endometrial biopsy as an outcome measure (Archer 1999, Archer 2001, Arrenbrecht 2004, Byrjalsen 1992a,Campodonico 1996, Chen 1999, Christensen 1982, Gulhan 2004, Hagen 1982, Jaisamrarn 2002, Jirapinyo 2003, Kazerooni 2004, Limpaphayom 2000, Liu 2005, Marslew 1991, Marslew 1992, Mizunuma 1997, Morabito 2004, Odmark 2001, Simon 2001, Simon 2003, Stevenson 2001, Wang 2006, Warming 2004a, Williams 1990). Four studies were subsequently found to be non-randomised (Granberg 2002, Nachtigall 1979, Sturdee 1996, Wahab 2002) and six had a treatment period less than one year (Keil 2002, Luciano 1988, Symons 2000, Symons 2002, Utian 2002, Yang 2001). Three studies included women with endometrial hyperplasia at baseline, (Campbell 1977, Popp 2006, Volpe 1986) which is an exclusion criteria for this review; in one study all the participants underwent transcervical resection of the endometrium at baseline (Istre 1996), and another publication (Steiner 2007) was a comparison of subgroups selected retrospectively from two previously conducted randomised studies which drew participants from very different populations. A study published in 1982 (Schiff 1982) compared a now obsolete cyclic estrogen-only regimen with a continuous estrogen-only regimen, and therefore did not meet the inclusion criteria for this review. A further four studies were found by handsearching and published in abstract form only. These publications contained insufficient information to establish eligibility for inclusion in the review and attempts to obtain further information from the authors have been unsuccessful (Aoki 1990, Heytmanek 1990,Sturdee 1996,Ulla Timonen 2002). Four further studies located by handsearching and published in abstract form only are awaiting assessment pending further information from the authors (Pickar 2003, van de Weijer 2002, van der Mooren 1996, Webster 1996).

Risk of bias in included studies

Study design

The included trials ranged in size from 32 (Nand 1995) to 16,608 participants (WHI 2002). The three largest trials were WHI 2002 (16,608 participants), HOPE 2001 (2673 participants) and MSG 1994 (1724 participants). Twenty seven were multi centre trials and in the remaining 18 women were recruited from a single centre. All had a parallel group design. Nine trials had performed a power calculation for sample size and analysis was by intention to treat (ITT) (Bruhat 2001; Greenwald 2005; Kurman 2000; Mattsson 2004; OGEN-Provera 1998; PEPI 1995; Portman 2003; Warming 2004; WHI 2002), three trials had power calculations and no ITT analysis (CHART 1996; MSG 1994; HOPE 2001) two studies did not provide power calculations but noted that the planned sample size "probably lacked power" (Ettinger 1992; Williams 1994) and another was a pilot study (Nand 1995). In thirty studies no mention of a power calculation was made. Twenty one studies used either a placebo control group or a placebo instead of one of the hormones in order to maintain blinding.

Allocation

All 45 trials were randomised but in 25 no details were provided of the method of randomisation. Four trials used random number tables (AinMelk 1996,Byrjalsen 2000,Sporrong 1988, Warming 2004), and 15 trials used computerised randomisation. In the remaining trial (Stadberg 1996) blocked randomisation was used but no further details were given on the method. Twenty eight

trials were classified with an allocation score of B (unclear allocation concealment). The remaining 17 trials were classified as A; adequate concealment prior to allocation.

Blinding

Thirty five of the forty five included trials used double blinding for most of the participants (in three studies Byrjalsen 2000; Rees 2004; Rozenberg 2001 some of the participants had open label treatment) two trials were single blinded (Byrjalsen 1992; Yildirim 2006) and in four trials blinding was not clear (Heikkinen 1997;Portman 2003;Scandinavia 1996;Wu 2002). Unblinding occurred in 38 women in the PEPI trial (31 of those receiving the unopposed estrogen regimen, four receiving one of the estrogen and progestogen regimens and three receiving placebo) because of endometrial biopsy results classified as complex hyperplasia, atypia or cancer. Unblinding also occurred in the WHI trial: 331 participants were unblinded and reassigned to the experimental group due to the release of the PEPI trial results indicating long term adherence to unopposed estrogen was not feasible in women with a uterus. The WHI protocol was subsequently changed to randomise women with a uterus to only estrogen plus progestogen or placebo in equal proportions.

Incomplete outcome data

Losses to follow up and withdrawals were common, particularly in the larger trials and trials with long duration. In the CHART study, 570 women (45%) had withdrawn (out of a total of 1265) by the conclusion of the trial at two years. In this trial, a priori stopping rules were applied for participants who developed hyperplasia and consequently a proportion of subjects in Group 8 (10 mcg daily of oral unopposed ethinyl estradiol (EE2) continuously) were terminated from the study early owing to a high rate of hyperplasia. All remaining treatment groups had similar rates of withdrawal that ranged from 22% to 30% and excluding the high dose estrogen group, over 73% of the subjects completed the study. Five other trials had more than 40% of women randomised withdraw prior to the end of the trial (Byrjalsen 1999; Ettinger 1992; Gelfand 1989; Greenwald 2005; Rees 2004). Details of the numbers of and reasons for early withdrawals are in the included studies table.

Where more than 20% of women who withdrew during the course of the study (due to adverse events or other reasons such as change of address, unwillingness to continue to participate) there was a correspondingly low rate of endometrial biopsy. High rates of withdrawals and/or losses to follow up thus reduced the power of the study to detect the primary outcome of interest to this systematic review.

- not statistically significantly increased compared to placebo (Table 4 continuous combined regimens and Table 5 sequentially combined regimens)

In tables 2-5, allocation concealment was used as an indication of overall risk of bias. Allocation concealment is only one aspect of study validity, and has the objective of avoiding selection bias. However, adequate allocation concealment is also strongly associated with the presence of double-blinding, and it may in addition be a marker for other bias-reducing strategies (Wood 2008). For more details on individual aspects of study quality, see Characteristics of included studies and risk of bias Figure 1.

Effects of interventions

We extracted data on the cumulative incidence of endometrial hyperplasia at 12, 24 and 36 months. Not all of the studies reported the incidence rates at these time intervals. No differentiation was made in the analysis between the type of hyperplasia (simple, atypical or complex), although this was reported in some studies. Where a study had only one comparison or control group and several different doses in the experimental group, we used subgroups only and did not combine the results, in order to avoid counting the control group more than once.

We have created four additional tables to summarise the lowest dose of progestogen added to various doses of estrogen which result in endometrial hyperplasia rates that are

- statistically significantly reduced compared to unopposed estrogen (Table 2 continuous combined regimens and Table 3 sequentially combined regimens)

(1) Unopposed estrogen versus placebo

- ***Low dose***

After one year of therapy there was no statistically significant difference in the rate of endometrial hyperplasia between the group receiving unopposed estrogen and the placebo group (4 RCTs OR 2.84 95% CI 0.97 to 8.29) Figure 2. However there was a statistically significant difference between the two groups in the rate of endometrial hyperplasia at 18-24 months, favouring the placebo group (6 RCTs OR 2.42 (95% CI 1.19 to 4.92)) Figure 3.

Figure 2. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.1 Endometrial hyperplasia at 1 year.

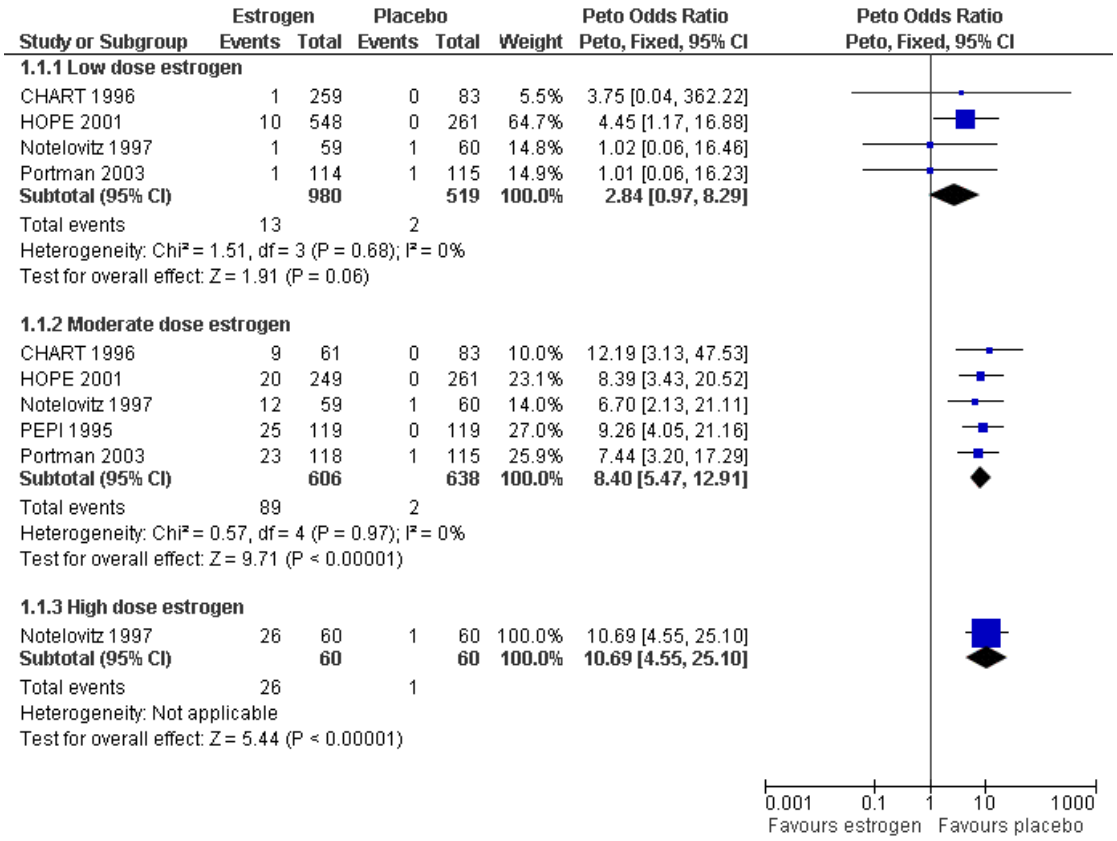
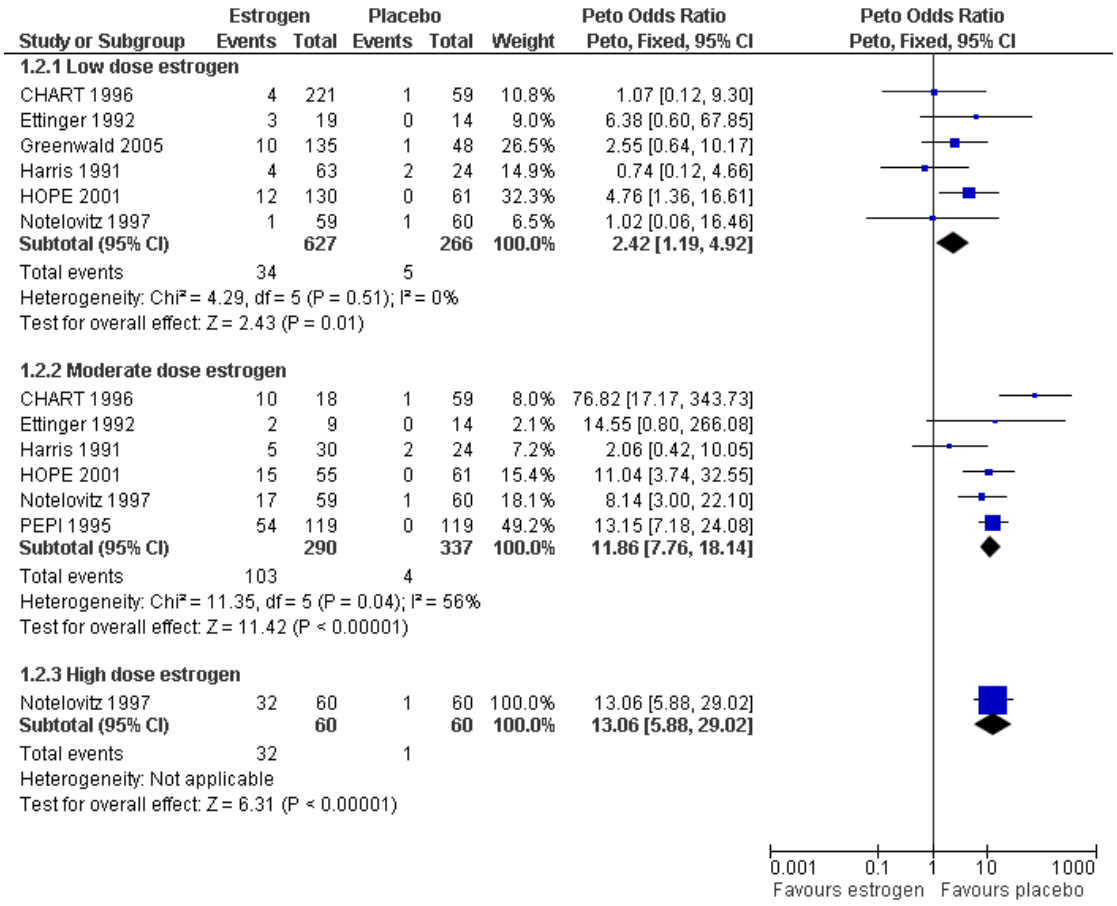


Figure 3. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.2 Cumulative endometrial hyperplasia at 18 - 24 months.



One trial with 591 participants (HOPE 2001) noted a statistically significant increase in the rate of endometrial hyperplasia when low doses of conjugated equine estrogen (either 0.3 mg or 0.45 mg) were compared with placebo. After 12 months follow up, there was a 1.8% rate of hyperplasia in the low dose unopposed groups (0% in the 0.3 mg CEE only group (n=74) and a 6.6% rate of hyperplasia in the 0.45 mg CEE group (n=76) with no hyperplasia in the placebo group). After 2 years these rates of endometrial hyperplasia increased to 9.2% for the combined low dose groups (3.2% in the 0.3 mg CEE group and 14.9 % in the 0.45 mg CEE group) with no hyperplasia in the placebo group.

The other trial, with 490 participants (CHART 1996), noted a 0.4% overall rate of endometrial hyperplasia after one year in the low dose estrogen groups (1-5 µg of ethinyl estradiol), compared to no cases of hyperplasia in the placebo group. In the CHART study after 2 years of therapy the low dose estrogen groups showed a 1.8% rate of endometrial hyperplasia which was not significantly different from the 1.7% placebo rate in this study.

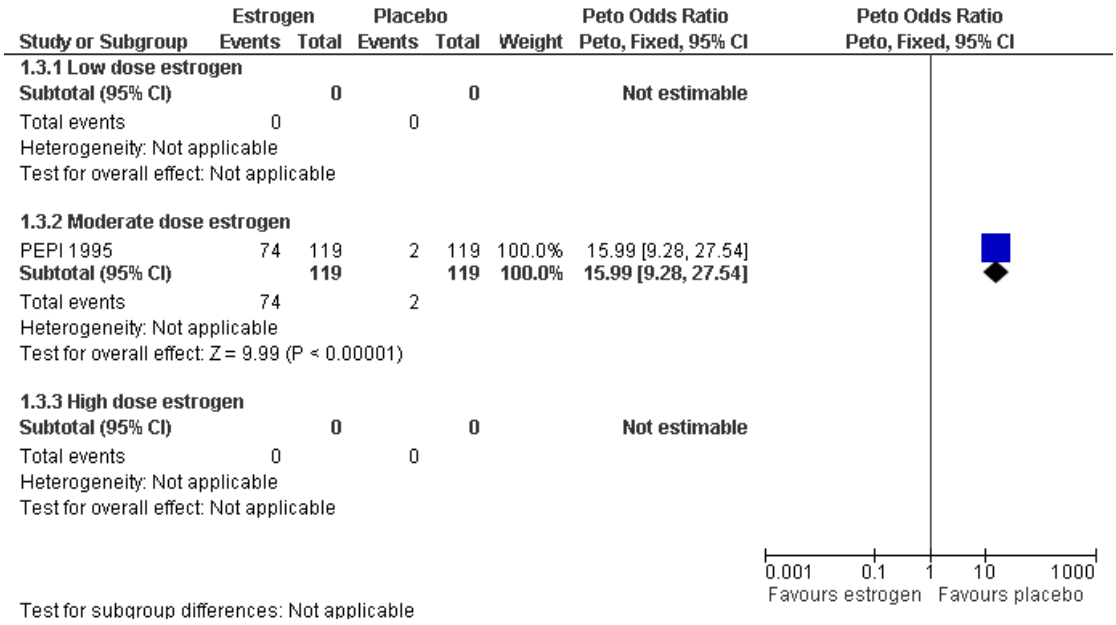
There were no cases of endometrial cancer detected in the one small study which assessed this outcome after two years of therapy (Notelovitz 1997).

There was no statistically significant difference in the rate of withdrawal due to adverse events between the low dose unopposed estrogen and placebo groups (4 RCTs OR 1.1 (95% CI 0.7 to 1.7)).

- ***Moderate Dose***

There were statistically significant differences in the rates of endometrial hyperplasia at 12 months (5 RCTs; OR 8.4 (95% CI 5.5 to 12.9)) Figure 2, 18-24 months (6 RCTs; OR 11.9 (95% CI 7.8 to18.1)) Figure 3 and 3 years (1 RCT; OR 16 (95% CI 9.3 to 27.5) Figure 4 in the studies that compared moderate dose unopposed estrogen therapy with placebo.

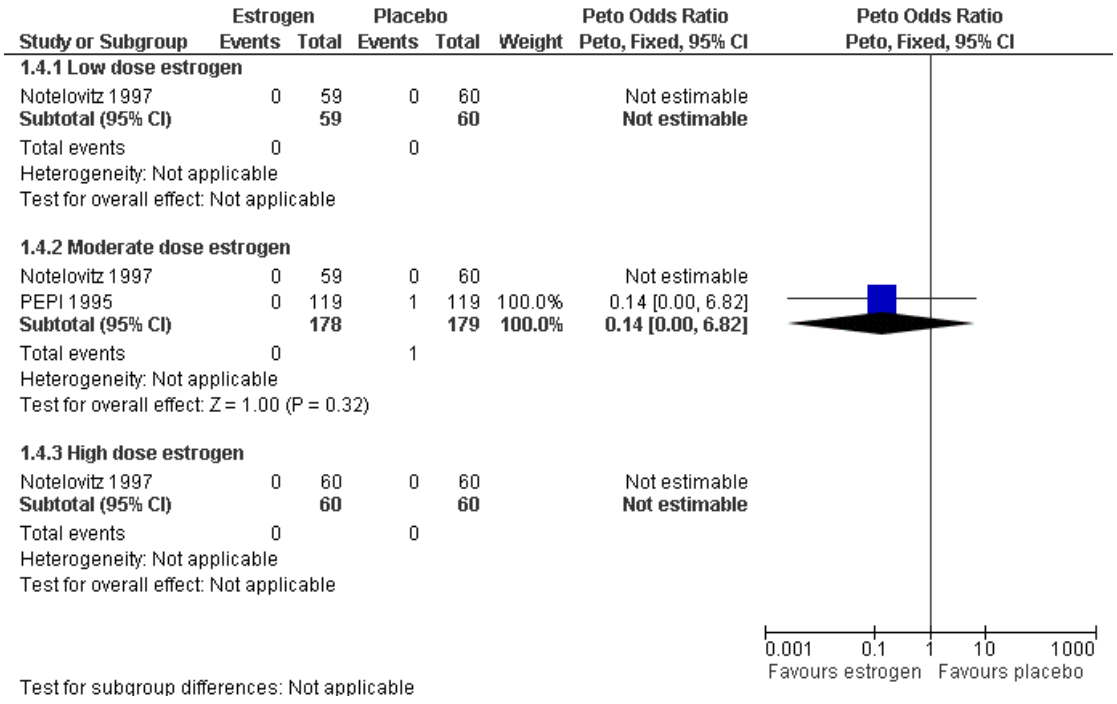
Figure 4. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.3 Cumulative endometrial hyperplasia at 3 years.



After one year of therapy, there were 89 cases of endometrial hyperplasia in the 606 women from 5 RCTs randomised to moderate dose unopposed estrogen (14.7%) compared to 2 cases in the 638 women randomised to placebo (0.3%) Figure 2. After 2 years of therapy there were 103 cases of endometrial hyperplasia in the 290 women randomised to moderate dose unopposed estrogen therapy (35.5%) compared to 4/337 or 1.2% of those randomised to placebo Figure 3. After 3 years, the PEPI 1995 trial showed a 62% rate of endometrial hyperplasia associated with moderate dose unopposed estrogen compared to 1.7% in the placebo group Figure 4 .

The only case of endometrial cancer in the 2 trials that assessed this outcome occurred in the placebo group Figure 5.

Figure 5. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.4 Endometrial Cancer 2-3 years.



There was a small statistically significant increase in adherence to therapy in the placebo group compared to the unopposed estrogen group in the one study (PEPI 1995) which assessed medication compliance (OR 0.2 (95% CI 0.1 to 0.36)) Figure 6. The only study that assessed the rate of unscheduled biopsies (PEPI 1995) found a significant increase associated with moderate dose unopposed estrogen therapy (1 RCT; OR 11.8 (95% CI 7.0 to 19.9)) Figure 7 .

Figure 6. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.5 Adherence to therapy at 1 year.

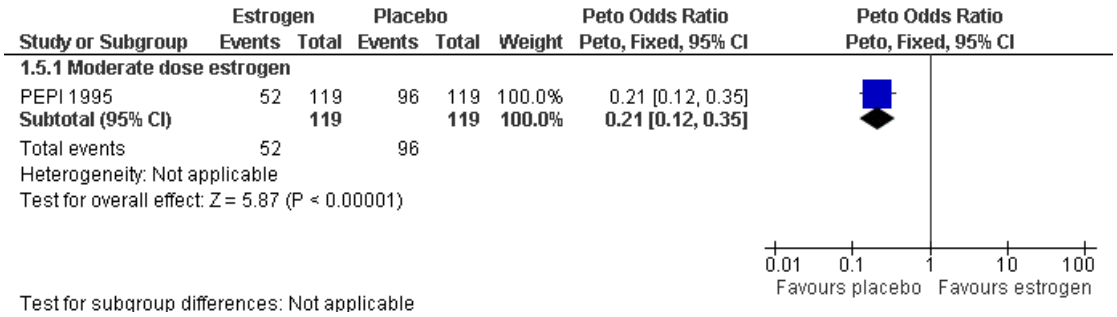
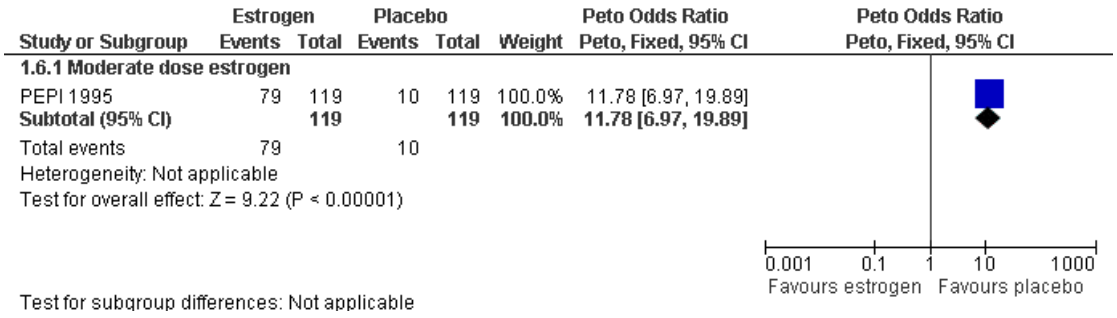
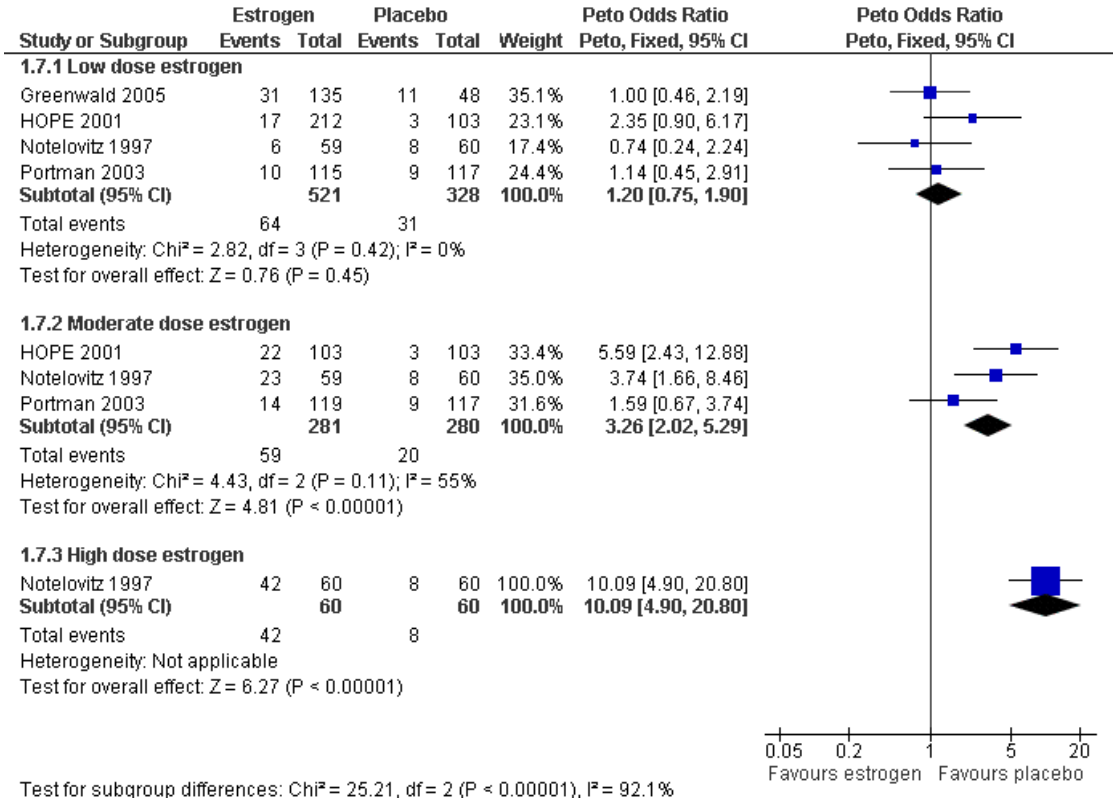


Figure 7. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.6 Additional investigations (unscheduled biopsy).



There was no statistically significant difference in the rate of early withdrawal from treatment due to adverse events in the moderate dose unopposed estrogen therapy group compared to the placebo group Figure 8 .

Figure 8. Forest plot of comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, outcome: 1.7 Withdrawals due to adverse events.



- ***High Dose***

In the only study (Notelovitz 1997) that compared high dose unopposed estrogen therapy with placebo the odds of developing endometrial hyperplasia at 12 months were significantly higher in the intervention group (OR 10.7 (95% CI 4.6 to 25.1)) Figure 2 and increased further at 18-24 months of therapy (OR 13.1 95% CI 5.9 to 29) Figure 3.

There were no cases of endometrial cancer in either the high dose unopposed estrogen or the placebo group after 2 years of therapy in this study Figure 5.

The odds of early withdrawal due to adverse events were significantly higher in the high dose unopposed estrogen group than in the placebo group (OR 6.8 95% CI 3.4 to 14.0) Figure 8. Vaginal bleeding and endometrial hyperplasia were the main reasons given for discontinuation in the high dose group.

(2) Estrogen + progestogen (continuous) versus placebo

In the 8 RCTs (Byrjalsen 2000; CHART 1996; Greenwald 2005; Obel 1993; PEPI 1995; Portman 2003; Warming 2004; HOPE 2001) which compared various doses and types of continuous combined E+P with placebo no statistically significant differences were found between any of the groups in the rates of endometrial hyperplasia after one, two or three years Figure 9; Figure 10; Figure 11. A summary of the lowest 'safe' dose of progestogens for endometrial protection for the various estrogen doses used can be found in Table 4

Figure 9. Forest plot of comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, outcome: 2.1 Endometrial hyperplasia at 1 year.

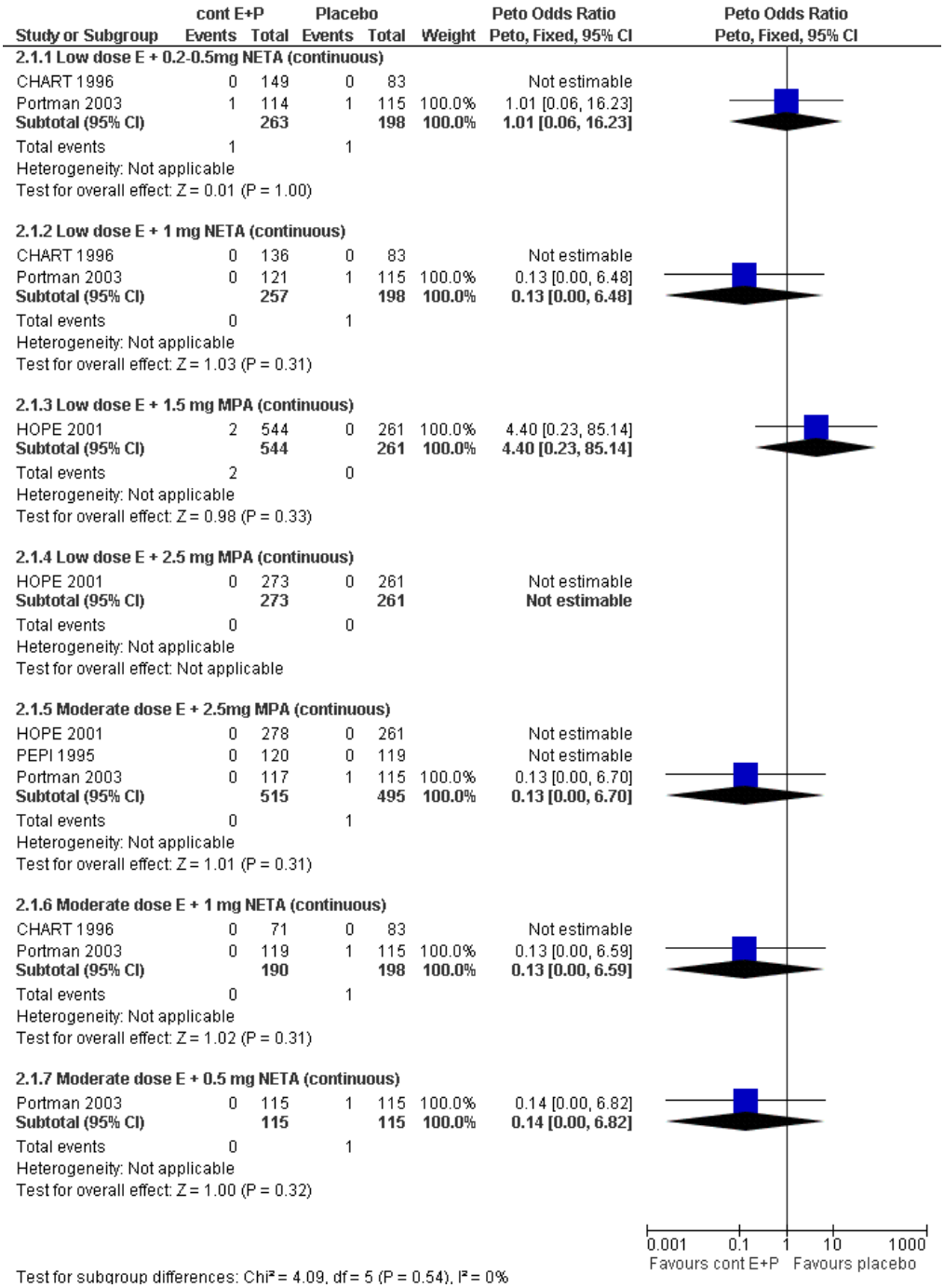


Figure 10. Forest plot of comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, outcome: 2.2 Cumulative endometrial hyperplasia at 2 years.

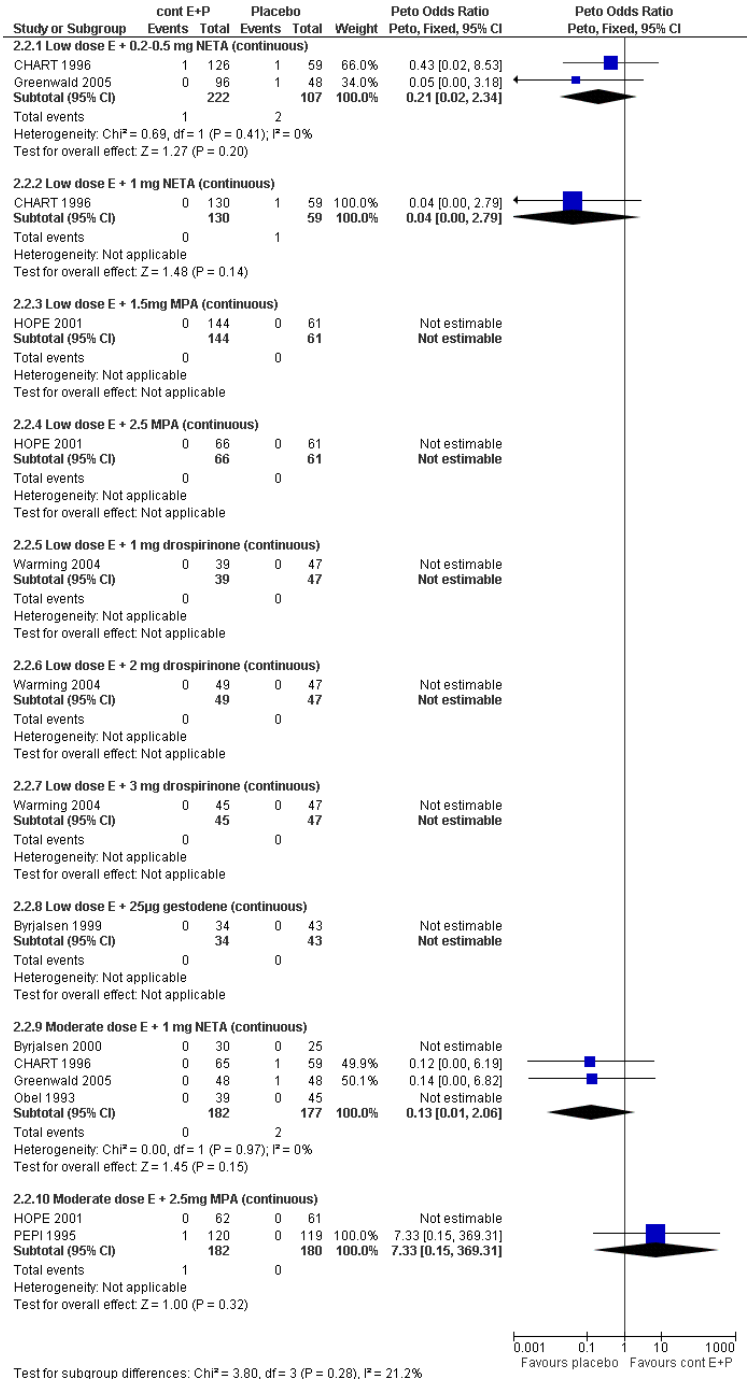
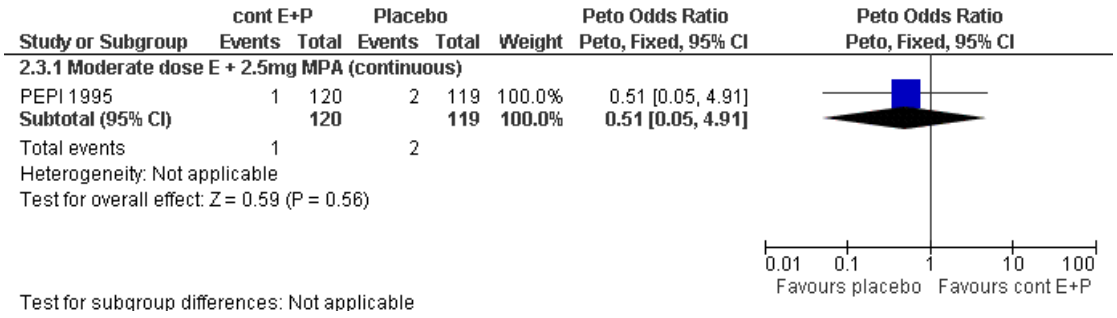
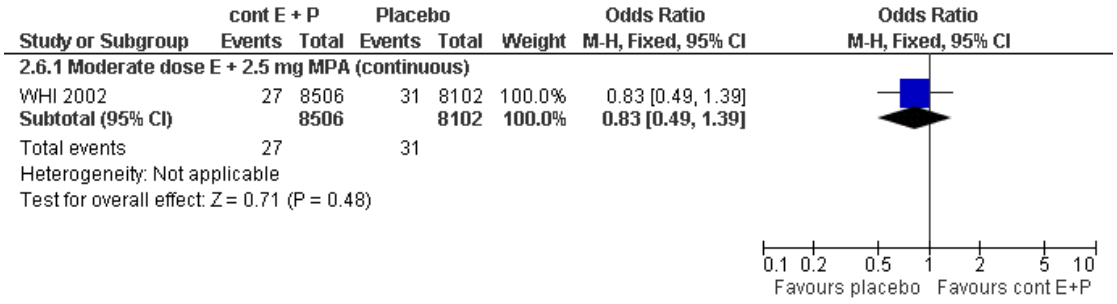


Figure 11. Forest plot of comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, outcome: 2.3 Endometrial hyperplasia at 3 years.



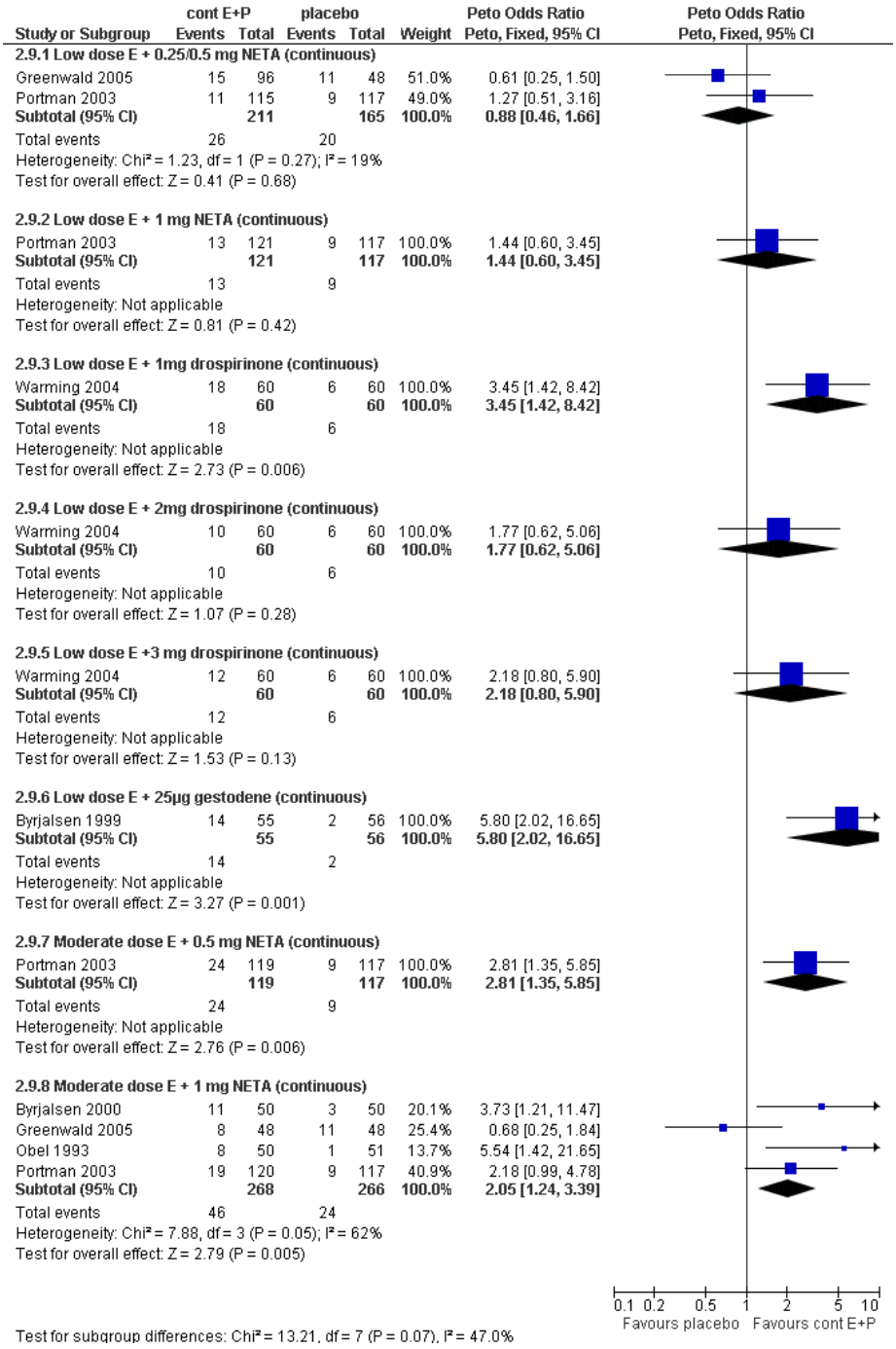
Similarly, rates of endometrial carcinoma were very low in the 4 studies that reported this outcome, with no statistically significant difference between the groups receiving continuous combined regimens and those on placebo, even after 5+ years of follow up (WHI 2002) Figure 12.

Figure 12. Forest plot of comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, outcome: 2.6 Cumulative endometrial cancer at 5+ years.



There was no evidence of a statistically significant difference between the groups in the odds of adherence to therapy, unscheduled biopsies or withdrawals due to adverse events Figure 13.

Figure 13. Forest plot of comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, outcome: 2.9 Withdrawals due to adverse events.

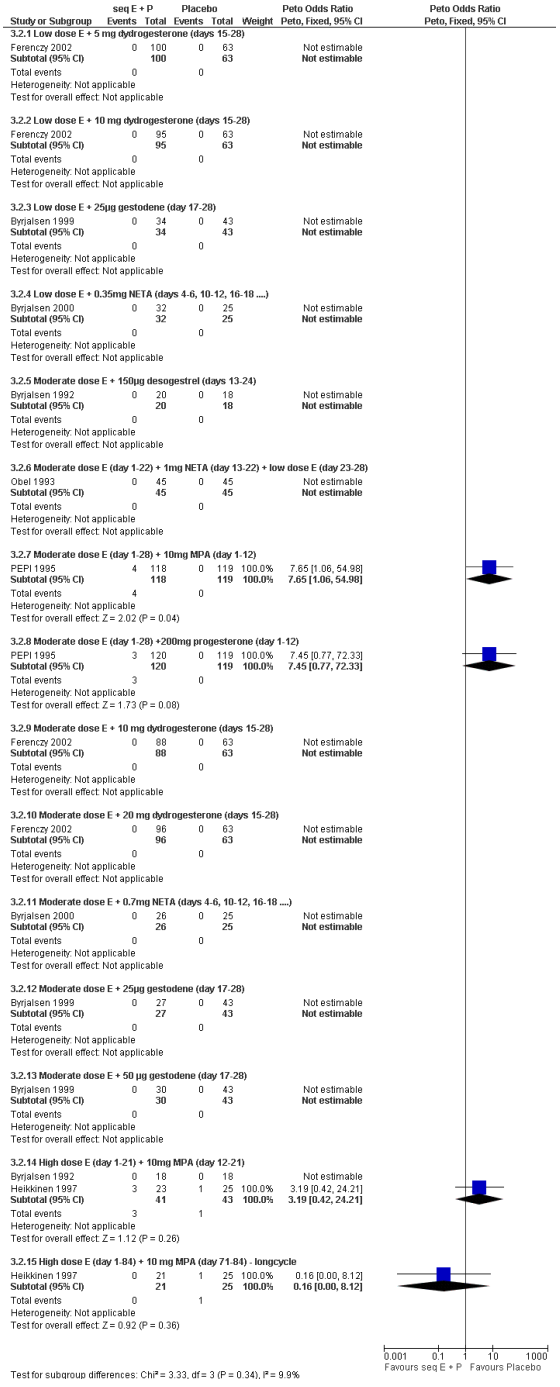


(3) Estrogen + progestogen (sequential) versus placebo

There were 8 RCTs included in this comparison (Byrjalsen 1992; Byrjalsen 1999; Byrjalsen 2000; Ferenczy 2002; Heikkinen 1997; Obel 1993; PEPI 1995).

There were no cases of endometrial hyperplasia associated with the low estrogen dose sequential regimens in 3 RCTs (Byrjalsen 1999; Byrjalsen 2000; Ferenczy 2002) over 2 years of treatment Figure 14.

Figure 14. Forest plot of comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, outcome: 3.2 Cumulative endometrial hyperplasia at 2 years.



In five of the RCTs that compared moderate estrogen dose sequential regimens with placebo (Byrjalsen 1992; Byrjalsen 1999; Byrjalsen 2000; Ferenczy 2002; Obel 1993) no cases of endometrial hyperplasia were found in either group Figure 14 . Regimens were as follows:

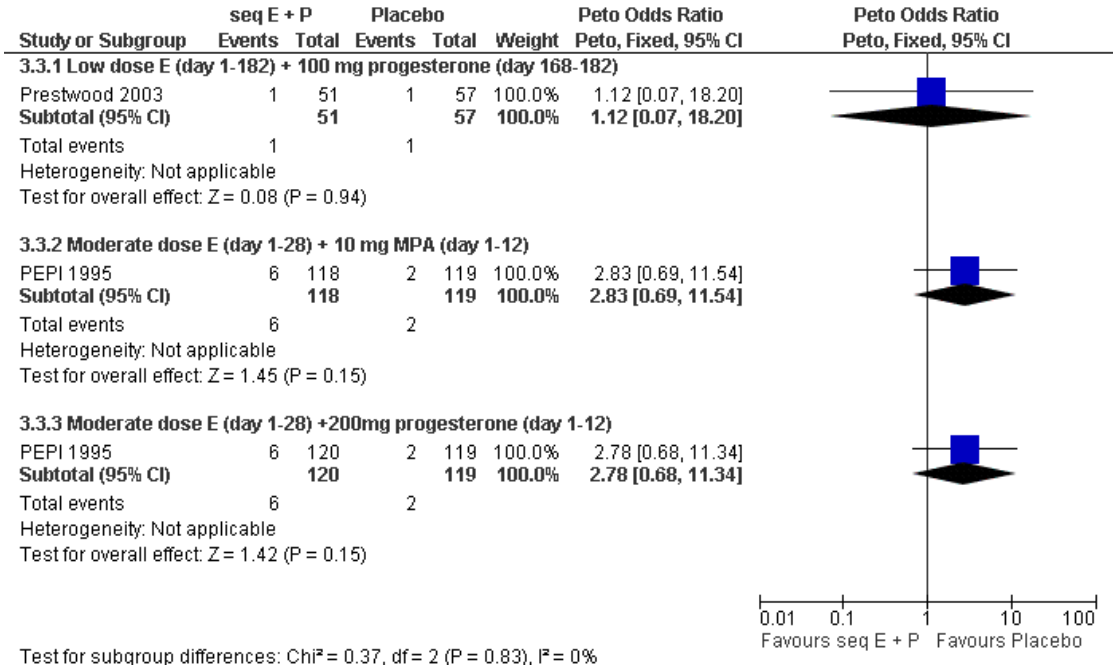
- 1.5 mg 17β estradiol plus 150 µg desogestrel for 14 days per cycle (Byrjalsen 1992)
- 2 mg estradiol plus 1 mg norethisterone acetate for 10 days per cycle (Obel 1993)
- 2 mg 17β estradiol plus 10 mg dydrogesterone for 14 days per cycle (Ferenczy 2002)
- 2 mg 17β estradiol plus 20 mg dydrogesterone for 14 days per cycle (Ferenczy 2002)
- 1.5 mg piperazine estrone sulphate plus 0.7 mg norethisterone (intermittent 3 days unopposed E, 3 days E+P) Byrjalsen 2000
- 2 mg estradiol plus 25 µg gestodene for 12 days per cycle (Byrjalsen 1999)
- 2 mg estradiol plus 50 µg gestodene for 12 days per cycle (Byrjalsen 1999)

In the PEPI 1995 study, 2 moderate estrogen dose sequential regimens were compared with placebo.

This study found a difference in odds of endometrial hyperplasia between placebo and a sequential regimen comprising 0.625 mg conjugated equine estrogens plus 10 mg medroxyprogesterone acetate for 12 days per cycle, that narrowly attained statistical significance after 2 years (OR 7.65 95% CI 1.06 to 54.98).The absolute risk of hyperplasia in the sequential regimen group was 3.3% compared to 0% in the placebo group. At 3 years follow up, there was no evidence of a statistically significant difference in rates of hyperplasia between the groups (OR 2.83,95% CI 0.7 to 11.5) for any sequential regimen (absolute risk with the MPA sequential regimen had increased to 5.1% compared to 1.7% in the placebo group) .

There was no statistically significant difference in the odds of developing endometrial hyperplasia after either 2 or 3 years of therapy in the group receiving the other sequential regimen utilised in PEPI 1995 (0.625 mg CEE plus 200 mg of micronised progesterone), compared to the placebo group Figure 15.

Figure 15. Forest plot of comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, outcome: 3.3 Cumulative endometrial hyperplasia at 3 years.



In the two studies that compared high dose estrogen sequential regimens with placebo (Byrjalsen 1992; Heikkinen 1997) there was no statistically significant difference between the groups in endometrial hyperplasia rates after 2 years of therapy Figure 15. There were no statistically significant differences between the groups in any of the included studies in the rates of endometrial cancer Figure 16 or additional investigations Figure 17 when sequential regimens were compared with placebo after 2 or 3 years of therapy.

Figure 16. Forest plot of comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, outcome: 3.5 Cumulative endometrial cancer at 3 years.

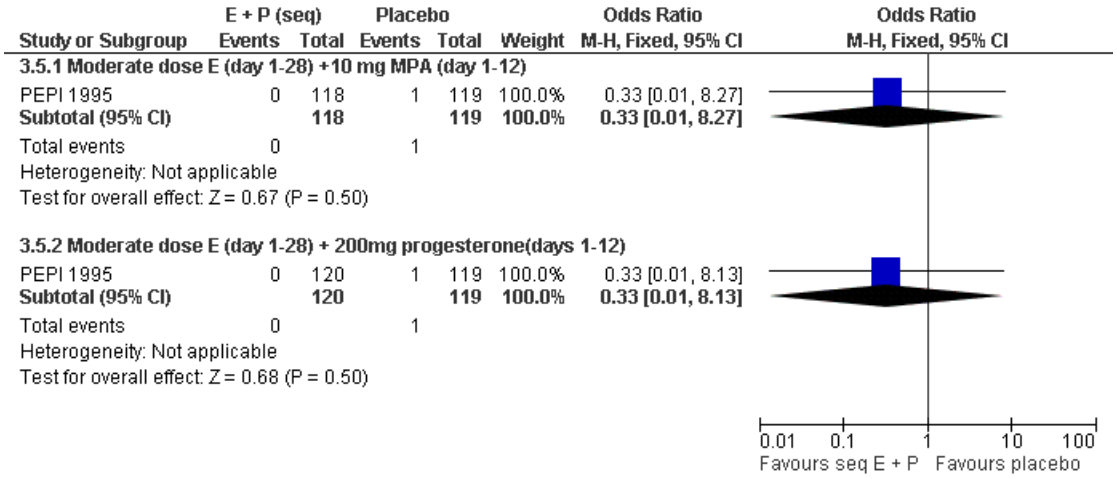
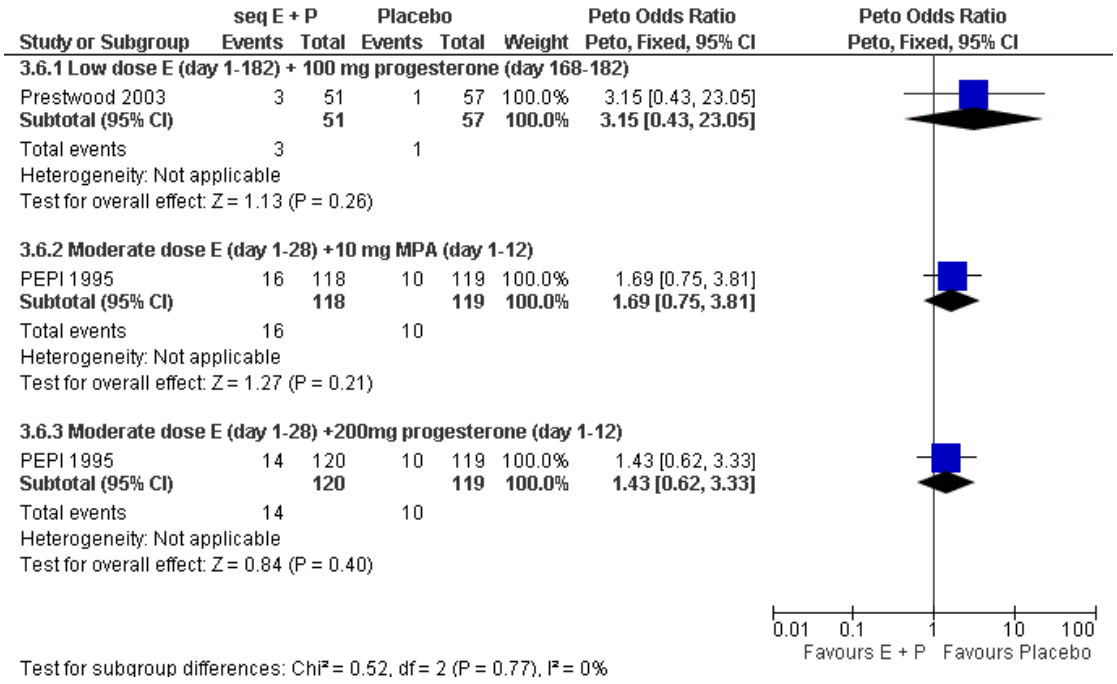
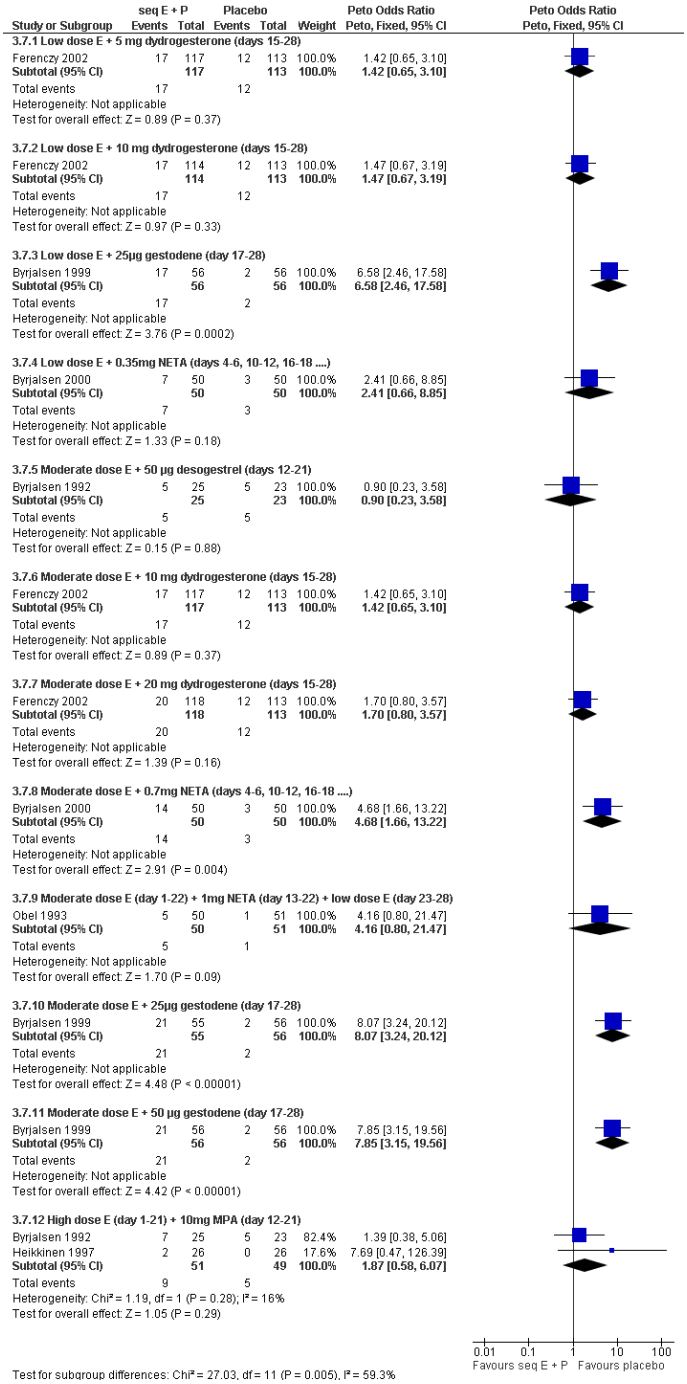


Figure 17. Forest plot of comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, outcome: 3.6 Additional investigations (unscheduled biopsy).



In the 6 RCTs that reported the outcome 'withdrawal due to adverse events' Figure 18, most of the regimens showed no statistically significant difference between the intervention and placebo groups. However the odds of withdrawal due to adverse events were higher in the groups receiving the following regimens:

Figure 18. Forest plot of comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, outcome: 3.7 Withdrawal due to adverse events.



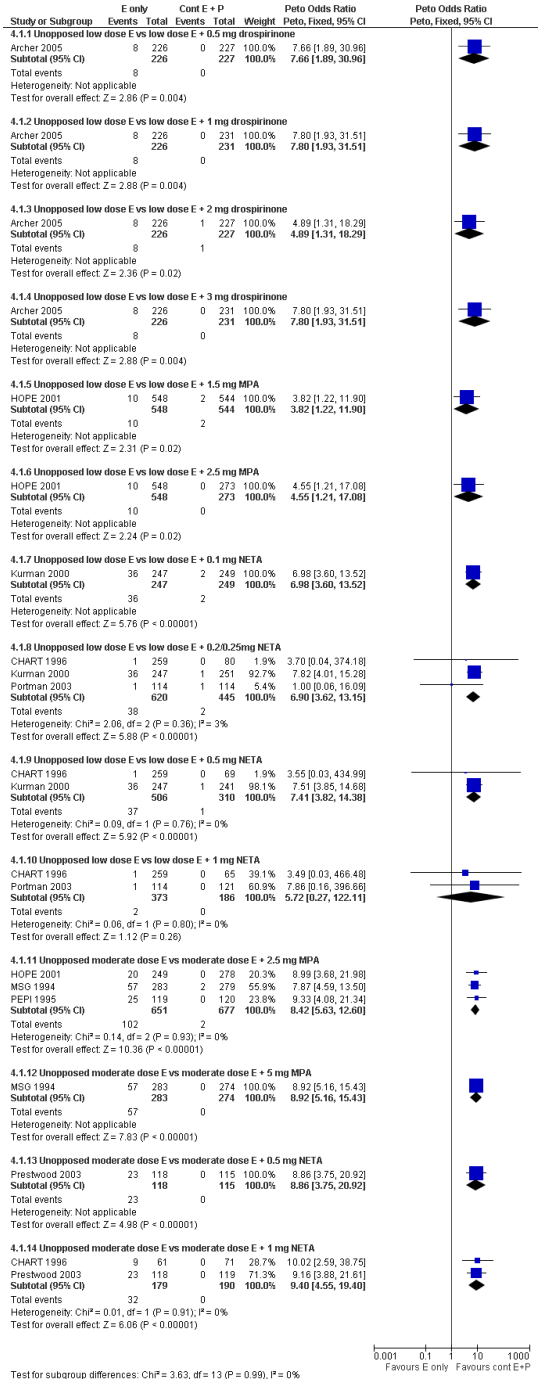
- 2 mg estradiol plus 25 µg or 50 µg gestodene for 12 days per cycle (Byrjalsen 1999)
- 1 mg estradiol plus 25 µg gestodene for 12 days per cycle (Byrjalsen 1999)
- 1.5 mg piperazine estrone sulphate plus 0.35 mg norethisterone acetate taken intermittently (3 days on 3 days off) (Byrjalsen 2000)

In both RCTs uterine bleeding was a common reason for early withdrawal.

(4) Unopposed estrogen versus estrogen + progestogen (continuous)

In six trials (Archer 2005; CHART 1996; Kurman 2000; MSG 1994; PEPI 1995; HOPE 2001), rates of endometrial hyperplasia after 1 year of therapy were significantly higher for the group receiving low or moderate dose unopposed estrogen therapy, compared with the group receiving continuous combined low or moderate dose E + P treatment, for all of the 13 regimens compared, with odds ratios for the individual comparisons ranging between 3.8 and 9.4. The summary odds ratio was not calculated because the same control group was used in more than one subgroup in these comparisons Figure 19.

Figure 19. Forest plot of comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), outcome: 4.1 Endometrial hyperplasia at one year.



After one year of continuous combined therapy the groups receiving following regimens containing low dose estrogen:

- 1 mg 17β estradiol plus either 0.5,1,2,or 3 mg drospirinone (Archer 2005)
- 1 mg 17β estradiol plus 0.1, 0.25, 0.5 mg NETA (Kurman 2000)
- 0.3 mg conjugated equine estrogens plus 1.5 mg MPA (HOPE 2001)
- 0.45 mg conjugated equine estrogens plus 2.5 mg MPA (HOPE 2001)
- 1µg or 2.5µg ethinyl estradiol plus 0.2 or 0.5 mg NETA (CHART 1996)

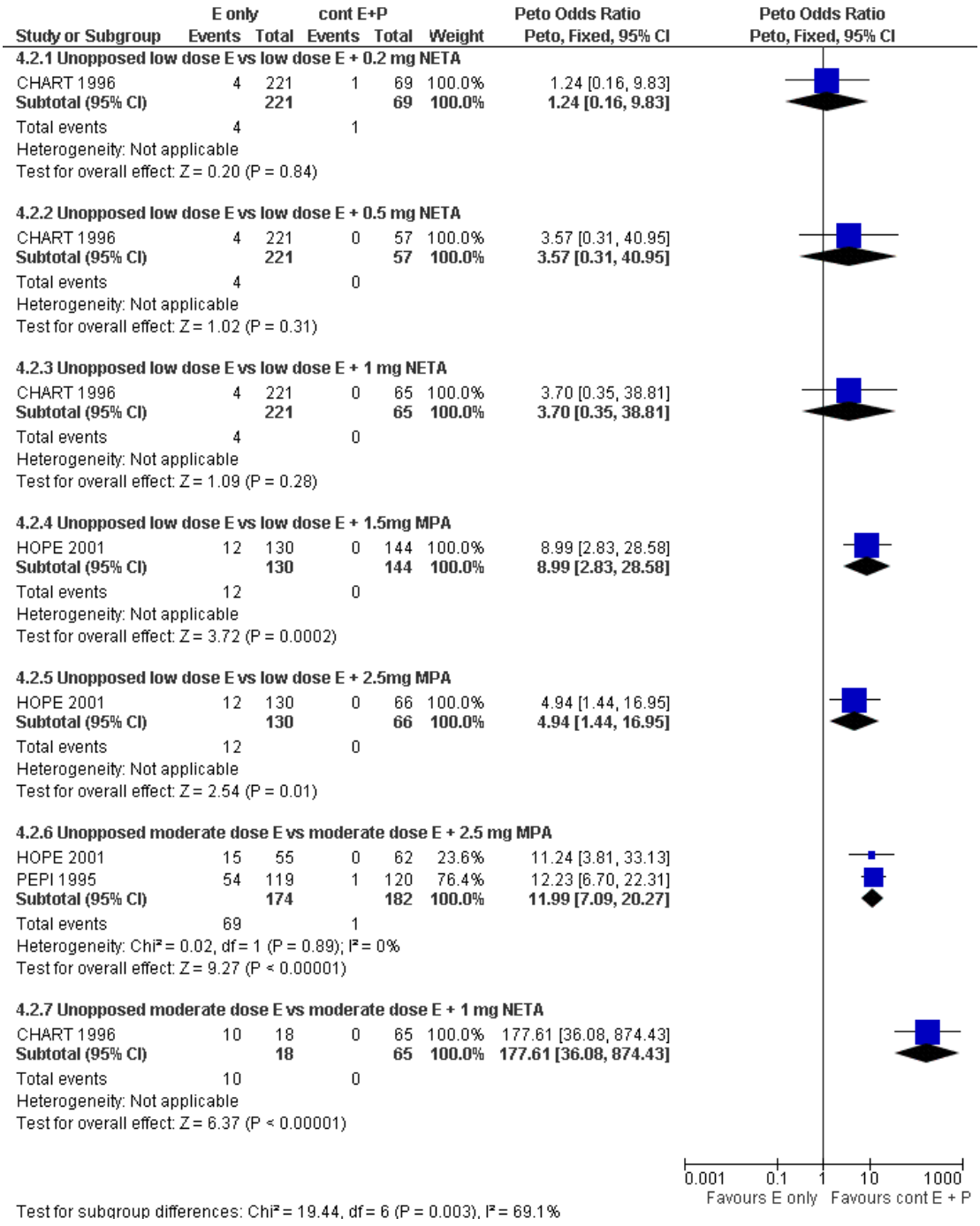
showed a statistically significant reduction in the odds of hyperplasia compared to the groups receiving low dose unopposed estrogen.

After 2 years of therapy, the statistically significant decrease in rate of endometrial hyperplasia was still evident for groups receiving the following low dose estrogen regimens:

- 0.3 mg conjugated equine estrogens plus 1.5 mg MPA (HOPE 2001)
- 0.45 mg conjugated equine estrogens plus 2.5 mg MPA (HOPE 2001)

but there was insufficient statistical power to determine the endometrial safety of the 1µg to 5 µg ethinyl estradiol plus 0.2mg to 1 mg NETA regimens Figure 19; Figure 20.

Figure 20. Forest plot of comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), outcome: 4.2 Cumulative endometrial hyperplasia at 2 years.

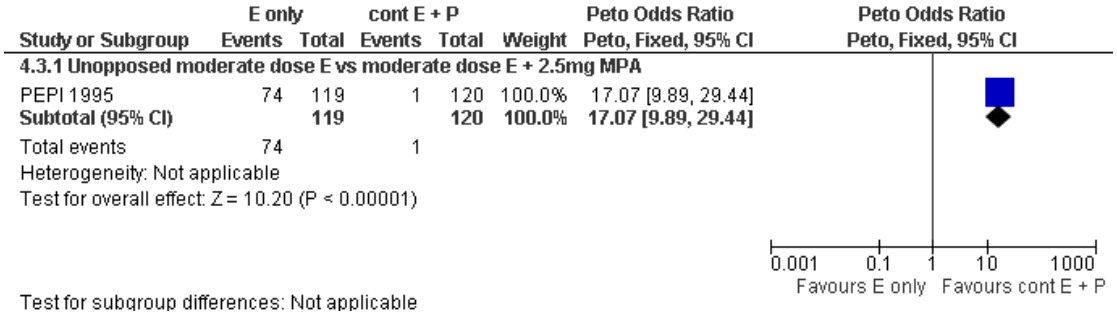


Groups receiving the following regimens containing a moderate dose of estrogen:

- 0.625 mg CEE plus either 2.5 or 5 mg MPA (HOPE 2001; MSG 1994; PEPI 1995)
- 10 µg ethinyl estradiol plus 1 mg NETA (CHART 1996)

showed a statistically significant reduction in odds of endometrial hyperplasia compared to groups receiving moderate dose unopposed estrogen after one or two years of therapy Figure 20 and the PEPI 1995 study showed that the reduced odds of endometrial hyperplasia persisted after 3 years of therapy Figure 21 .

Figure 21. Forest plot of comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), outcome: 4.3 Cumulative endometrial hyperplasia at 3 years.



There were three RCTs that compared unopposed estrogen with continuous combined E+P with regard to the outcome of endometrial cancer. After one year of therapy there were no cases of endometrial cancer in either group in Kurman 2000, which compared low dose unopposed estrogen only with low dose estrogen plus 0.1- 0.5 mg NETA, and there was only one case of endometrial cancer in MSG 1994 in the unopposed estrogen group. However this study lacked sufficient power to show a statistically significant difference between the groups with regard to the outcome of endometrial cancer after one year of therapy. PEPI 1995 reported no cases of endometrial cancer in either the moderate dose estrogen only group or the moderate dose estrogen plus 2.5 mg MPA group after 3 years of therapy.

Adherence to therapy as measured by pill counts showed a small but statistically significant increase in the continuous combined estrogen and progestogen group compared to the groups receiving unopposed estrogen (1 RCT; OR 0.2 (95% CI 0.1 to 0.3) and unscheduled biopsies were more likely under unopposed estrogen treatment (1 RCT; OR 12.4, 95% CI 7.4 to 21.0).

Withdrawals due to adverse effects were significantly higher in the unopposed estrogen group (1 RCT; OR 2.3, 95% CI 1.4 to 4.0).

(5) Unopposed estrogen versus estrogen + progestogen (sequential)

In this comparison sequential combined hormone therapy included intermittent regimens where women took estrogen alone for three days, followed by estrogen plus progestogen for three days, then estrogen alone for 3 days (repeated for a year), and also the more common regimen where progestogen was added for 11 or 12 days per cycle.

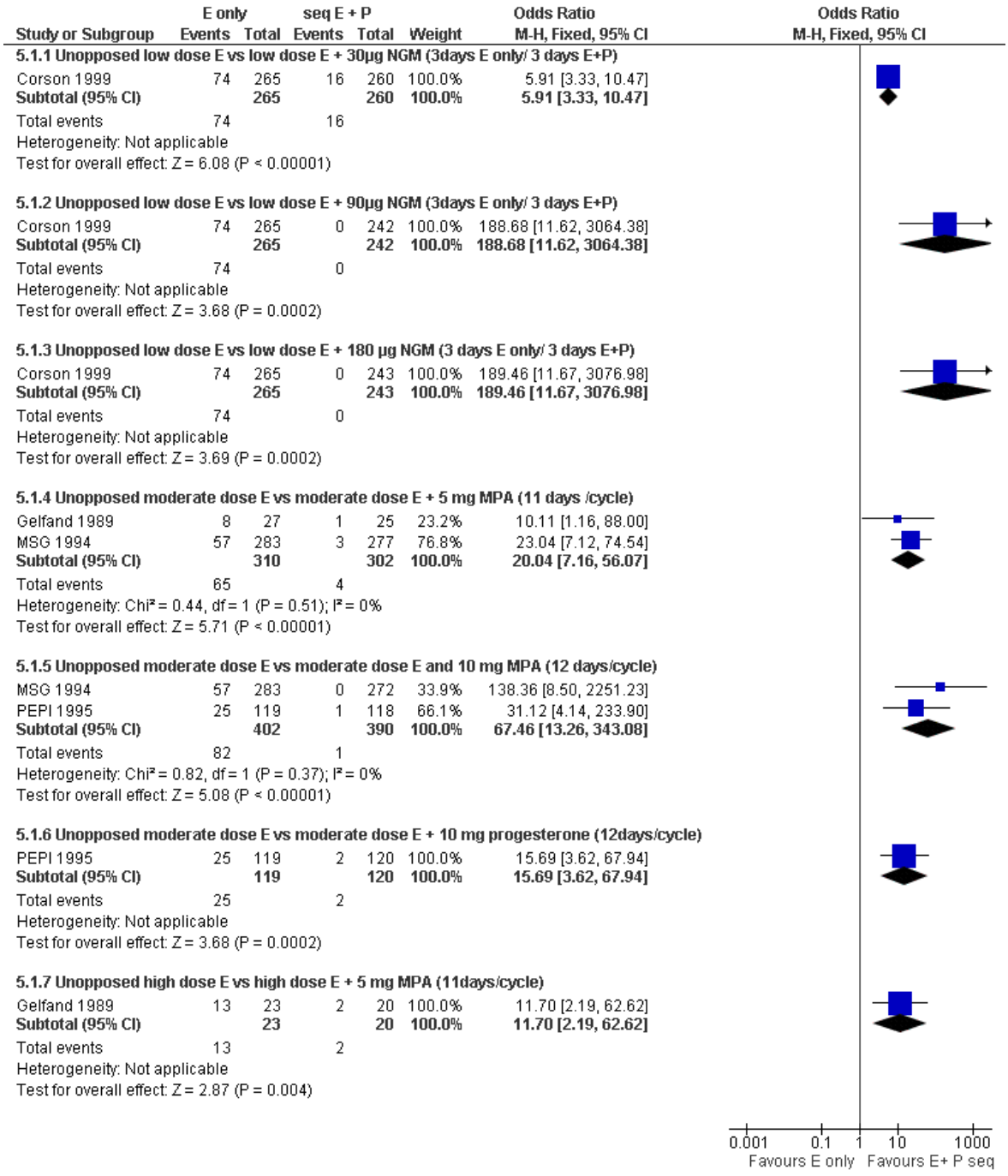
Four RCTs (Corson 1999; Gelfand 1989; MSG 1994; PEPI 1995) compared sequential E+P regimens with unopposed estrogen using the following doses and regimens:

- 1mg 17β estradiol plus 30 µg norgestimate (intermittent 3 days on/ 3 days off) (Corson 1999)
- 1mg 17β estradiol plus 90 µg norgestimate (intermittent 3 days on/ 3 days off) (Corson 1999)
- 1mg 17β estradiol plus 180 µg norgestimate (intermittent 3 days on/ 3 days off) (Corson 1999)
- 0.625 mg conjugated equine estrogens plus 5 mg medroxyprogesterone acetate (11-12 days per cycle) (Gelfand 1989; MSG 1994)

- 0.625 mg conjugated equine estrogens plus 10 mg medroxyprogesterone acetate (12 days per cycle) (MSG 1994; PEPI 1995)
- 1.25 mg conjugated equine estrogens plus 5 mg medroxyprogesterone acetate (11 days per cycle) (Gelfand 1989)

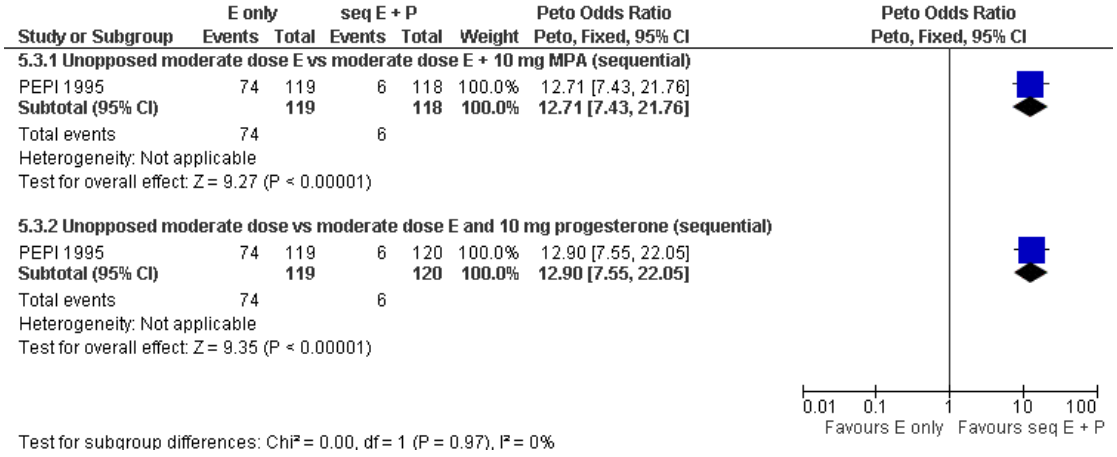
There were statistically significant differences in the odds of developing endometrial hyperplasia at one year between the groups taking unopposed estrogen and the groups taking sequential estrogen plus progestogen in all of the regimens compared, favouring the sequential group Figure 22. These are summarised in Table 3 .

Figure 22. Forest plot of comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), outcome: 5.1 Endometrial hyperplasia at one year.



Only one study (PEPI 1995) followed women treated for more than one year and found that a sequential regimen with 10 mg of either medroxyprogesterone acetate or micronised progesterone given for 12 days per cycle was associated with a statistically significant decrease in the odds of endometrial hyperplasia compared to an unopposed estrogen regimen (OR 12.8 (95% CI 8.8 to 18.8)) after 3 years of therapy Figure 23.

Figure 23. Forest plot of comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), outcome: 5.3 Cumulative endometrial hyperplasia at 3 years.

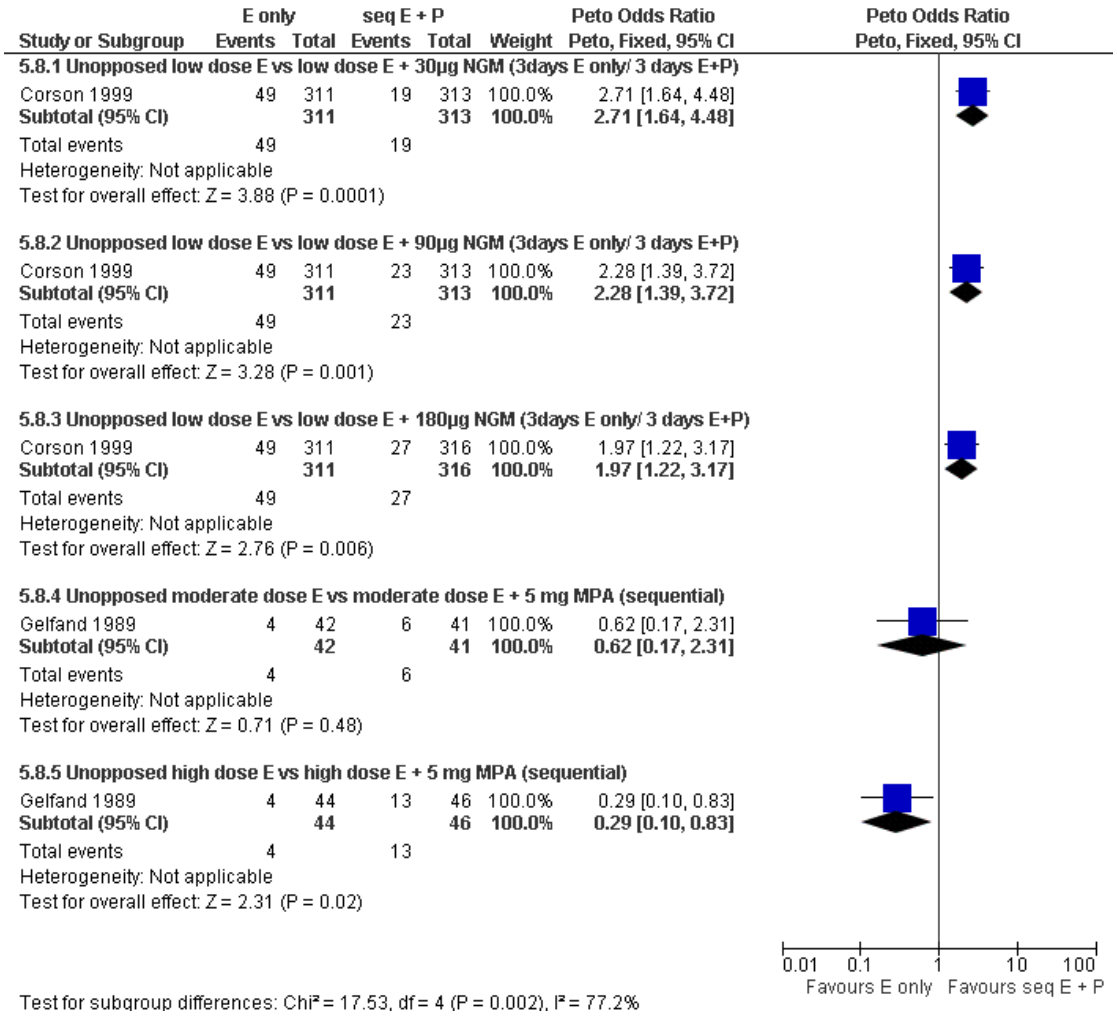


After one year of therapy there was no difference in the rate of endometrial cancer (one case in E only group and one in the E+MPA group) in the one study that reported this outcome (MSG 1994). After three years of hormone therapy the PEPI 1995 study reported no cases of endometrial cancer in either the unopposed estrogen or the sequential combined groups.

Unscheduled biopsies were more frequent in the estrogen only group in the only trial that reported these outcomes (PEPI 1995) and adherence to therapy was greater in the sequential combined groups compared to the unopposed E group in the same study.

Women were more likely to withdraw because of an adverse event in the unopposed estrogen group in one study which compared low dose unopposed estrogen with 3 different doses of an intermittent 3 days on/3 days off E+P regimen (Corson 1999). However in the other study that reported this outcome (Gelfand 1989) where unopposed estrogen was compared with a sequential regimen where MPA was added for 11 days per cycle, withdrawal due to adverse events were similar in both groups receiving moderate dose estrogen. In (Gelfand 1989) withdrawal due to adverse events was significantly more likely in the high dose sequential group compared to the unopposed high dose estrogen group (Figure 24).

Figure 24. Forest plot of comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), outcome: 5.8 Withdrawal due to adverse events.



(6) Estrogen + progestogen (continuous) versus estrogen + progestogen (sequential)

There were 6 RCTs which compared sequential combined therapy with continuous combined therapy (Byrjalsen 2000; Luciano 1993; MSG 1994; Obel 1993; PEPI 1995; Rozenberg 2001). The sequential therapy groups included regimens of 10 days progestogen per cycle (Obel 1993), 12 days progestogen per cycle (Luciano 1993;PEPI 1995), 14 days per cycle (MSG 1994) and regimens where progestogen was taken for 3 days followed by a 3 day break throughout the cycle (Rozenberg 2001; Byrjalsen 2000; (intermittent regimens). The odds of endometrial hyperplasia were not significantly different between the groups receiving continuous and the groups receiving sequential regimens of combined treatment at 12, 24 and 36 months for any of the comparisons included Figure 25; Figure 26; Figure 27.

Figure 25. Forest plot of comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), outcome: 6.1 Endometrial hyperplasia at 1 year.

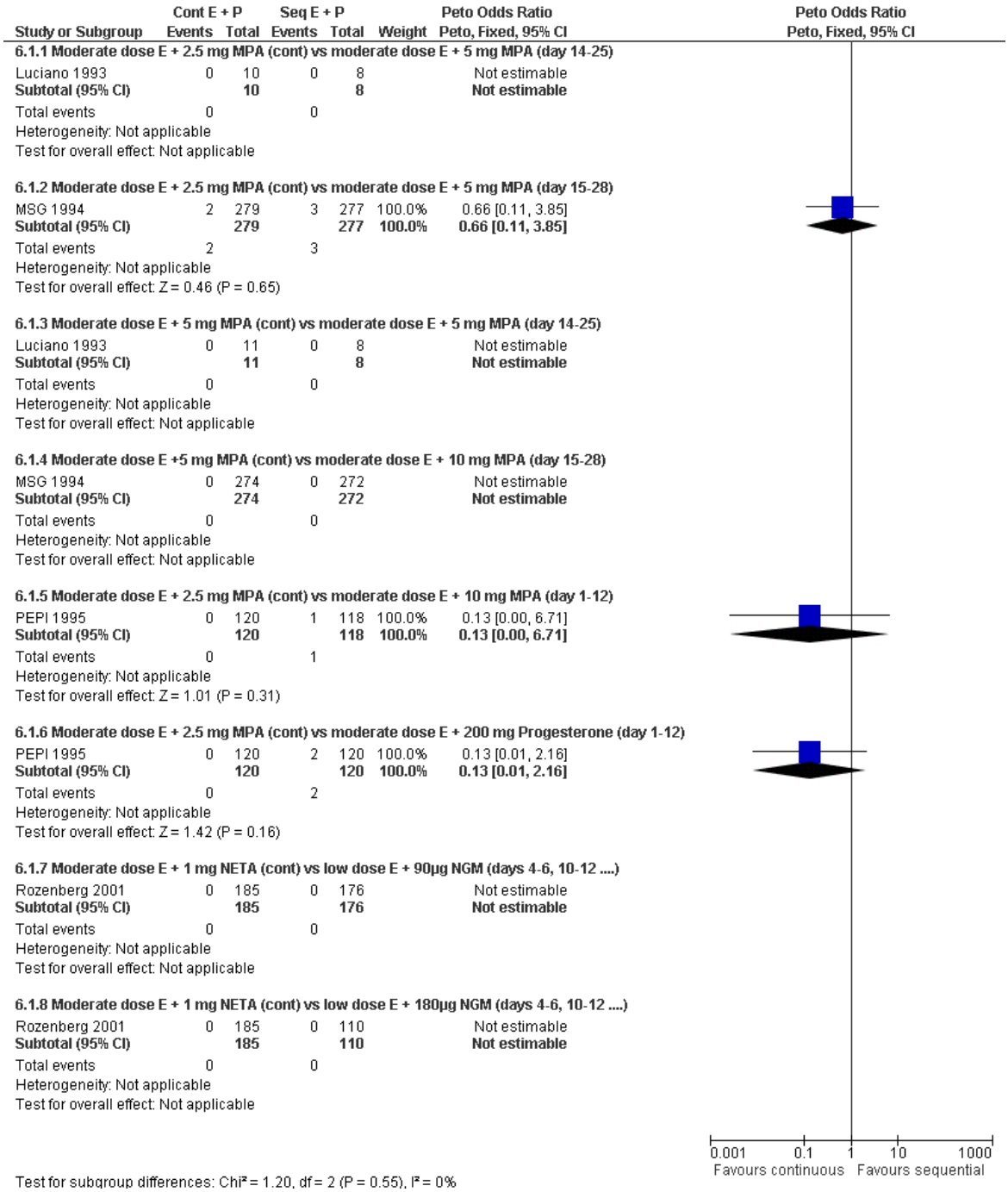


Figure 26. Forest plot of comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), outcome: 6.2 Cumulative endometrial hyperplasia at 2 years.

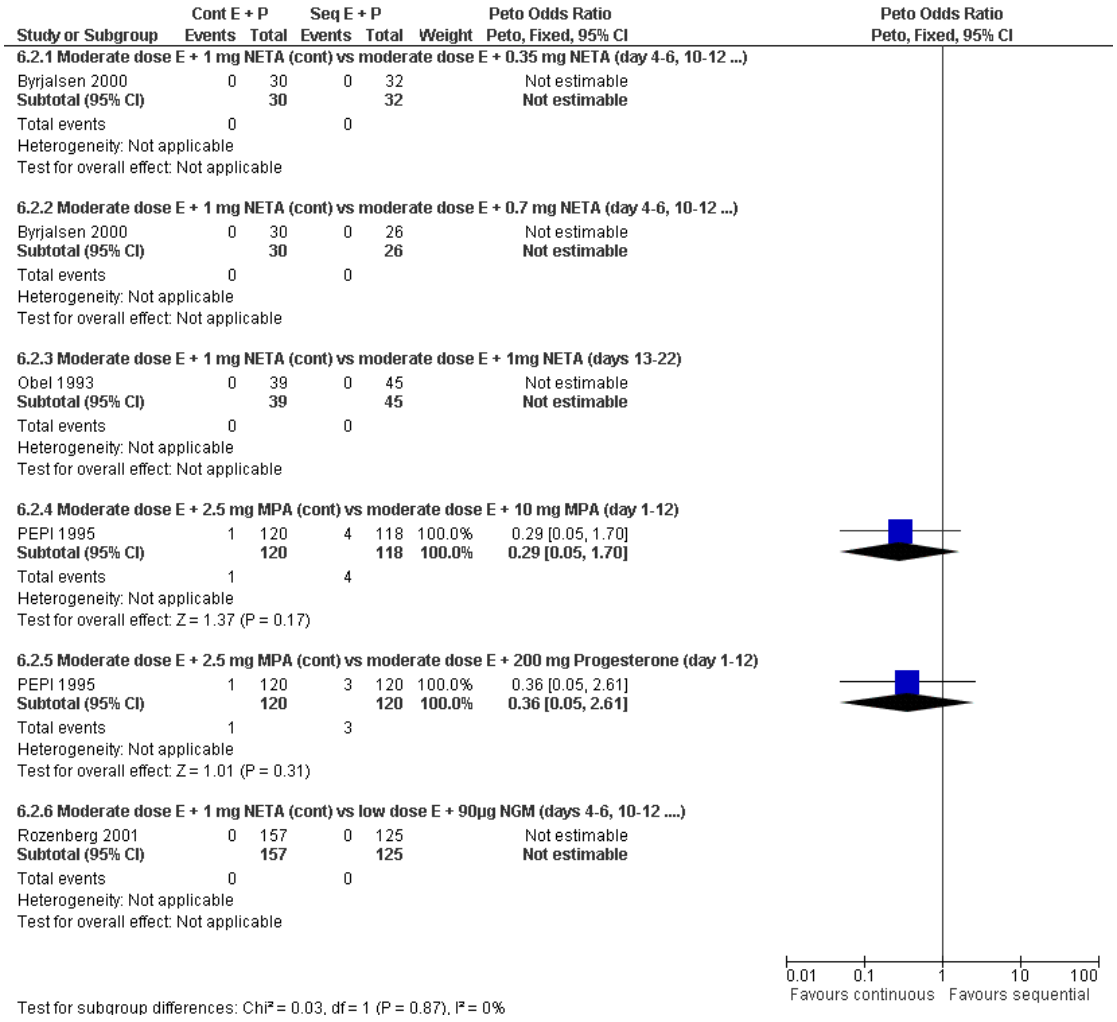
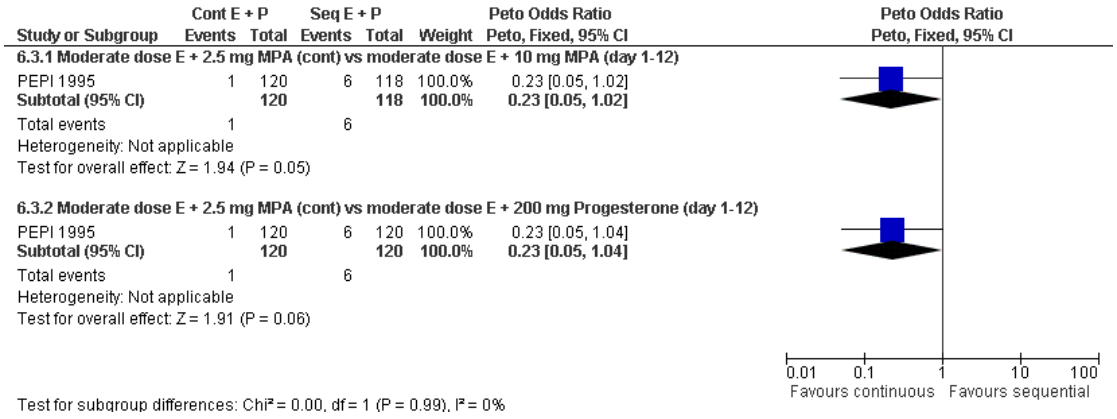


Figure 27. Forest plot of comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), outcome: 6.3 Cumulative endometrial hyperplasia at 3 years.



There were no statistically significant differences between the groups receiving continuous and sequential regimens in the rates of carcinoma, adherence to therapy Figure 28, additional investigations Figure 29 or withdrawal due to adverse events Figure 30.

Figure 28. Forest plot of comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), outcome: 6.7 Adherence to therapy.

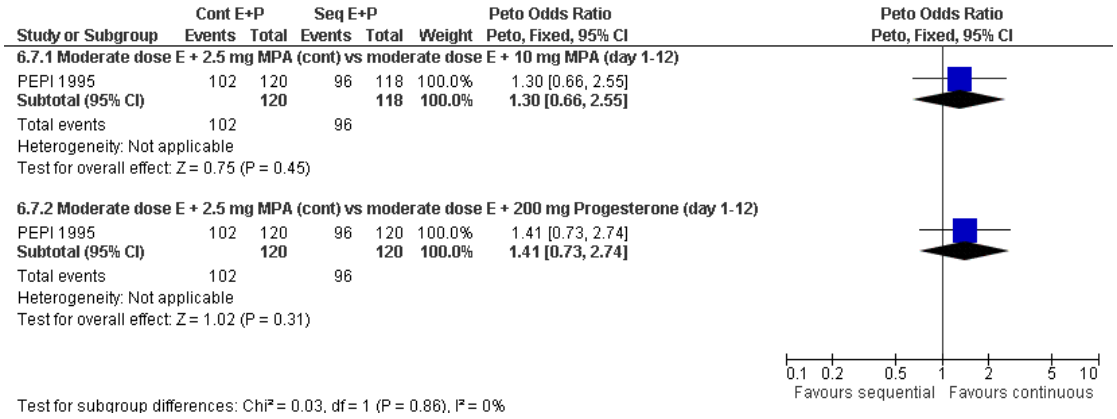


Figure 29. Forest plot of comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), outcome: 6.8 Additional Investigations.

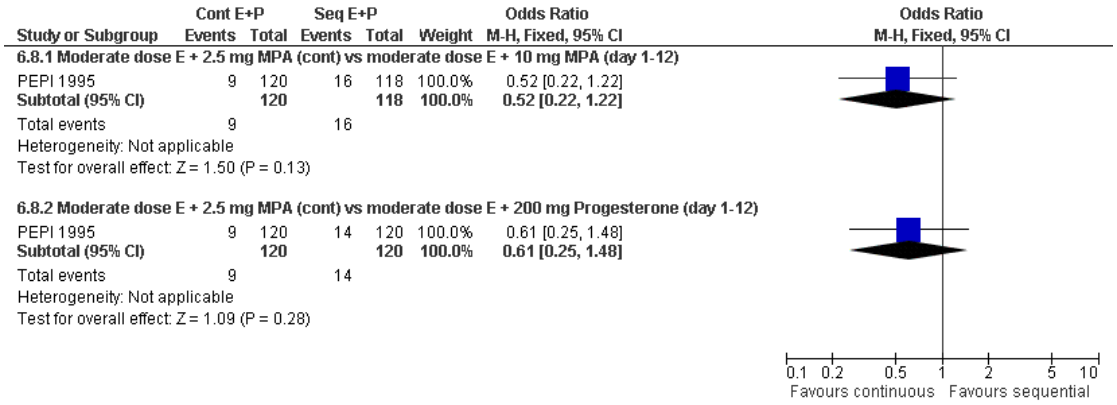
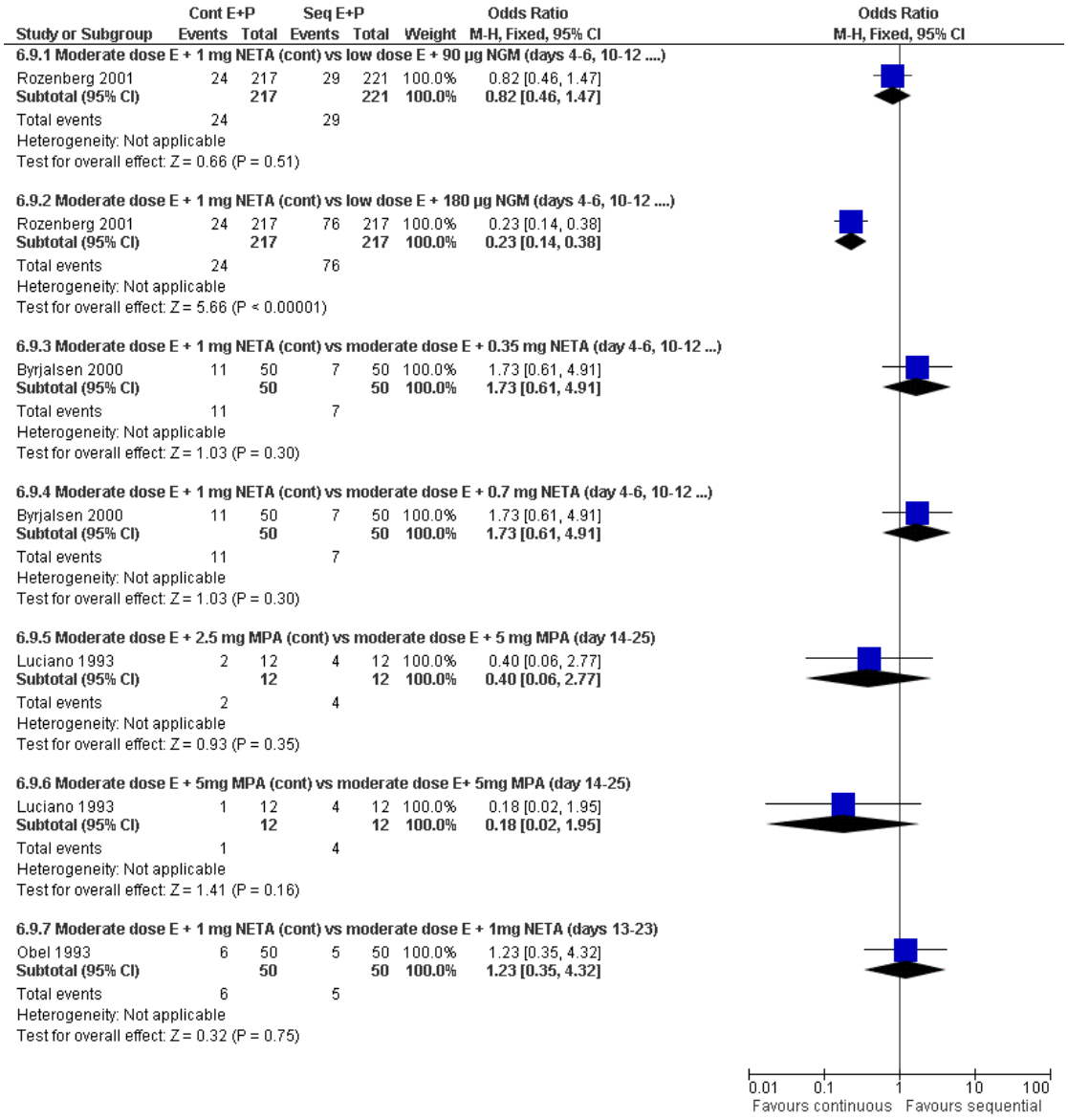


Figure 30. Forest plot of comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), outcome: 6.9 Withdrawal due to adverse events.



(7) Continuous combined estrogen + progestogen (dose/regimen comparisons)

There were 15 RCTs that compared various dose combinations of continuous combined hormone therapy:

- 6 RCTs (Archer 2005; Bouchard 2005;CHART 1996;Kurman 2000; Portman 2003; HOPE 2001) compared low dose estrogen combined with various doses of either drospirinone, trimegestone, medroxyprogesterone and norethisterone acetate
- 4 RCTs (AinMelk 1996; Greenwald 2005; Stadberg 1996;Yildirim 2006) compared low estrogen dose combinations with moderate estrogen dose combinations
- 3 RCTs (Sporrong 1988; MSG 1994;OGEN-Provera 1998) compared moderate estrogen doses combined with various doses of either norethisterone acetate, megestrol acetate, or medroxyprogesterone acetate.
- 2 RCTs (Bruhat 2001; Graser 2000) compared moderate to high estrogen doses combined with various doses of medroxyprogesterone acetate, norethisterone acetate or dienogest.

After one or two years of therapy there were no statistically significant differences in the rates of endometrial hyperplasia between groups receiving any of the doses compared in the 15 RCTs included Figure 31; Figure 32 .

Figure 31. Forest plot of comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), outcome: 7.1 Endometrial hyperplasia at 1 year.

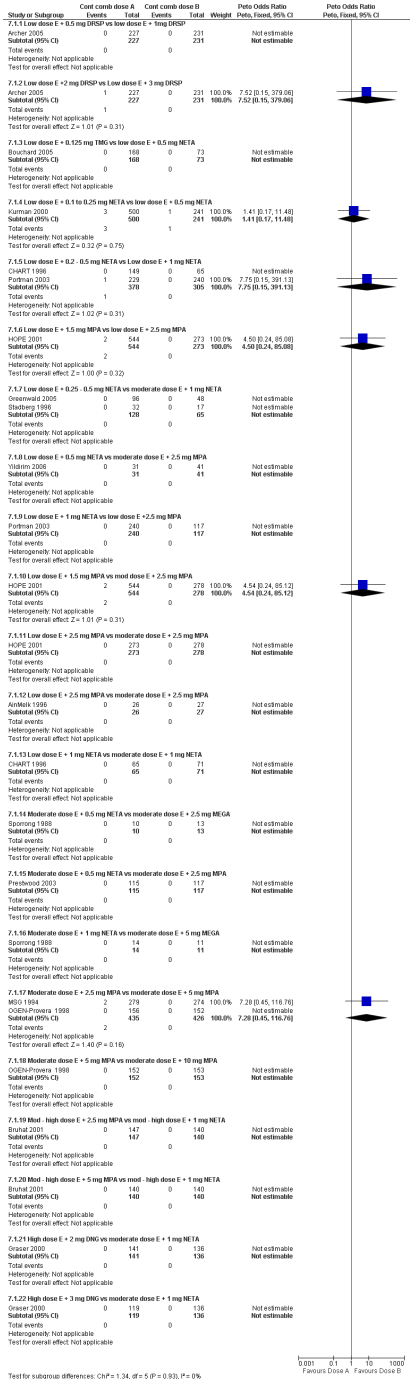
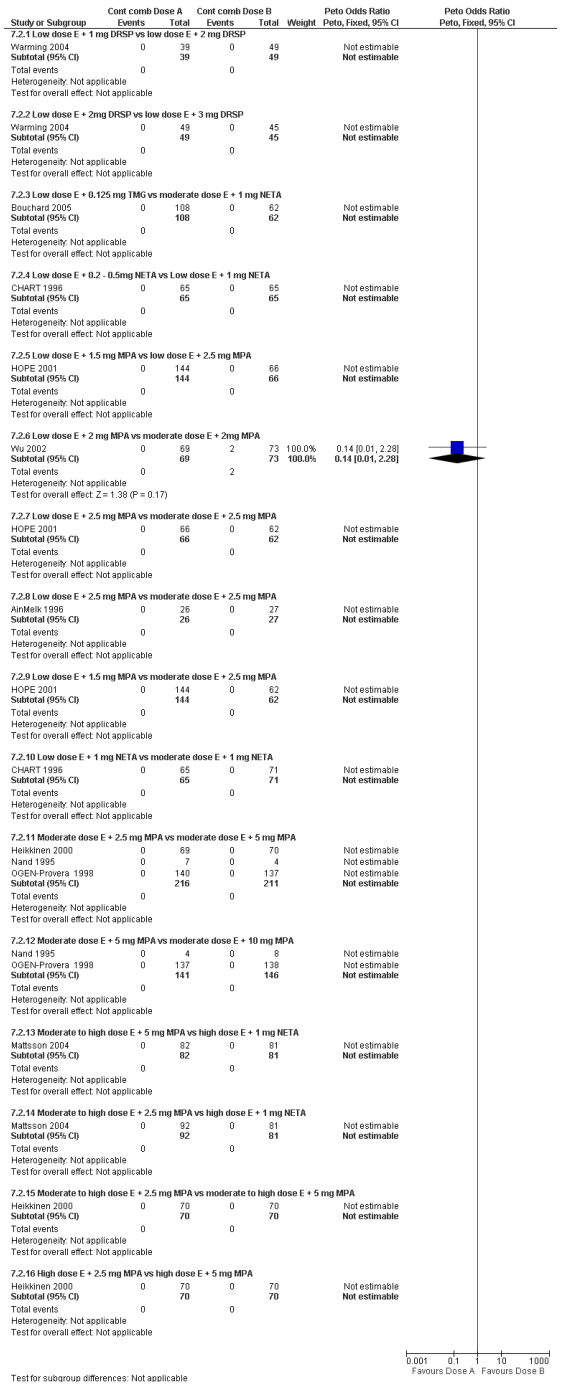


Figure 32. Forest plot of comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), outcome: 7.2 Cumulative endometrial hyperplasia at 2 years.



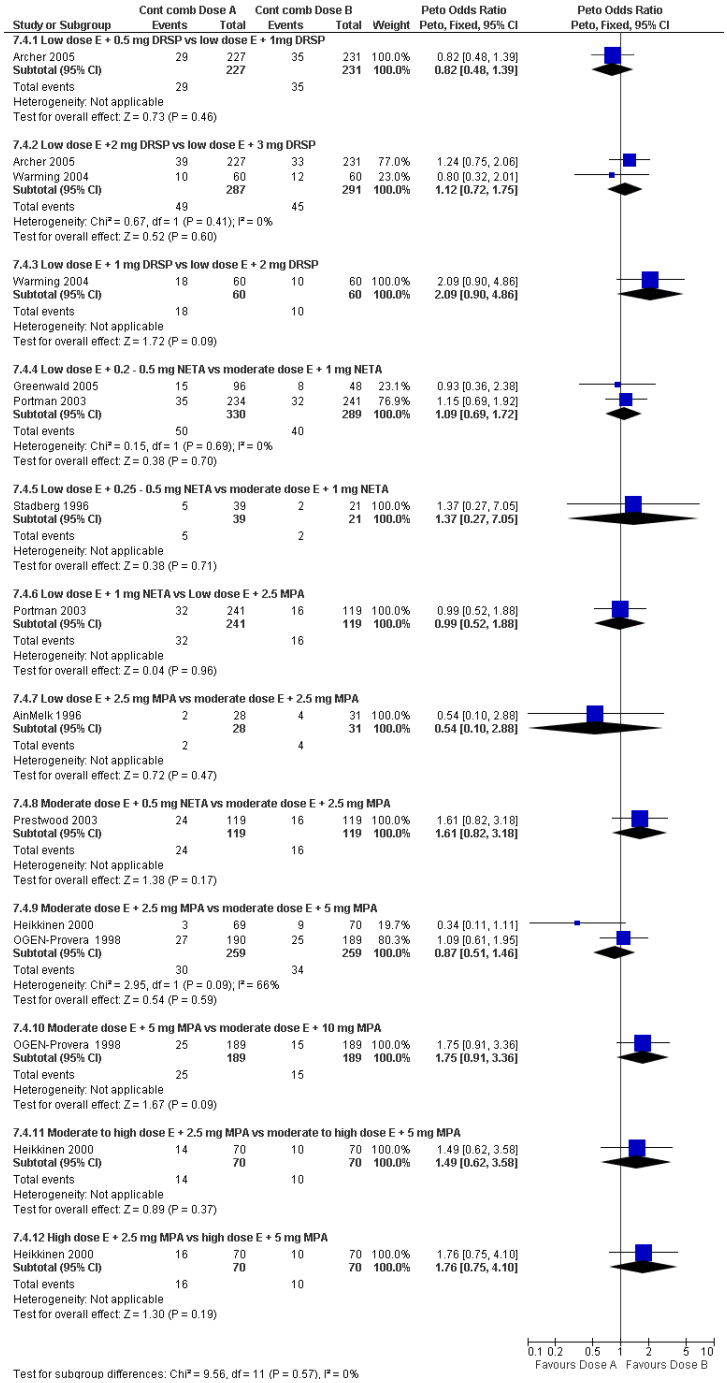
Regimens included the following dose ranges;

- low dose estrogen continuously combined with either 1-3 mg drospirinone, 0.1 to 1 mg NETA, 1.5 -2.5 mg MPA or 0.125 mg trimegestone
- moderate dose estrogen continuously combined with 1 mg NETA, 2.5 - 10 mg MPA or 2.5 - 5 mg MEGA
- high dose estrogen continuously combined with 2-3 mg dienogest.

All of the continuous combined regimens included were associated with low rates of hyperplasia (approximately 0.3% over one year). In the 2 RCTs that reported endometrial cancer, no cases were found after a year of therapy.

Withdrawal from the study due to adverse events was reported by eight RCTs and no statistically significant difference was found between the groups receiving any of the continuous combined regimens compared Figure 33.

Figure 33. Forest plot of comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), outcome: 7.4 Withdrawal due to adverse events.



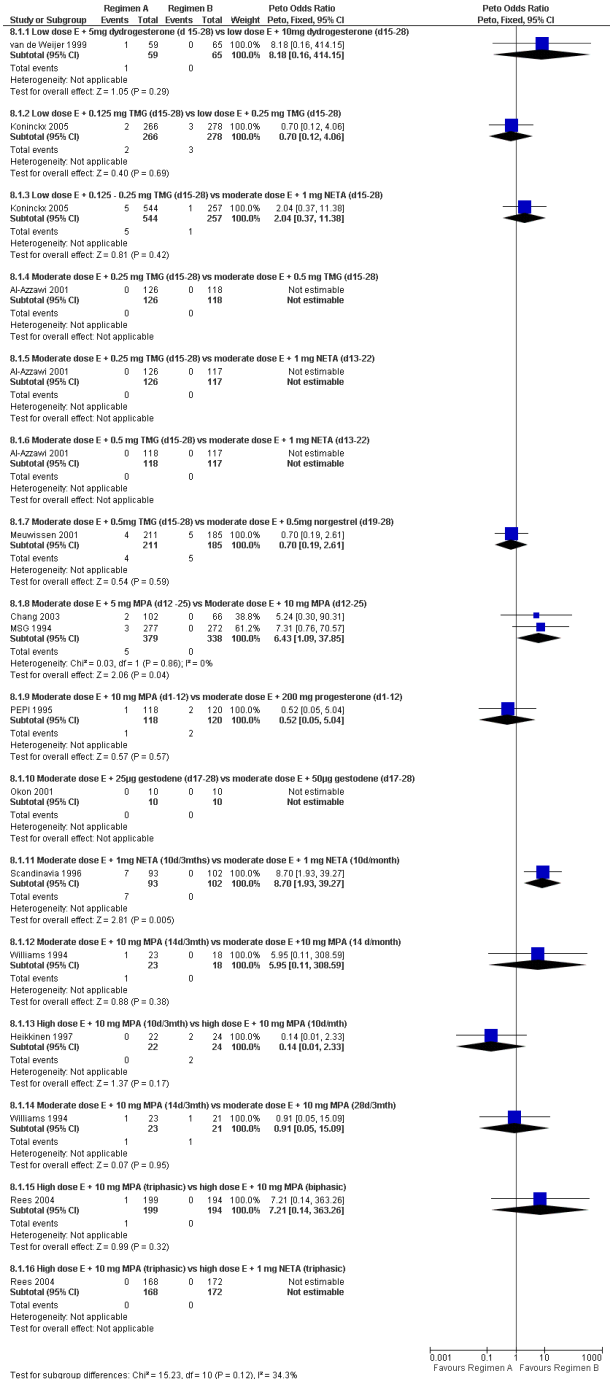
(8) Sequential combined estrogen + progestogen (dose/regimen comparisons)

There were 12 RCTs which compared different sequential regimens and doses of hormone therapy. The regimens compared fall into 5 major groups:

- 5 RCTs (Al-Azzawi 2001; Chang 2003; Koninckx 2005; MSG 1994; van de Weijer 1999) compared different doses of progestogens (trimegestone, dydrogesterone, MPA) taken for 14 days per monthly cycle
- 2 RCTs (Okon 2001; PEPI 1995) compared 12 days per monthly cycle of different progestogens.
- 2 RCTs (Al-Azzawi 2001; Meuwissen 2001) compared 14 days per cycle of trimegestone with 10 days of either NETA or norgestrel per cycle
- 3 RCTs (Heikkinen 1997; Scandinavia 1996; Williams 1994) compared long cycle sequential progestogen (for 10 - 28 days every 3 months) with progestogen given for 10-14 days per month, and one RCT Prestwood 2003 compared placebo with ultra low dose estrogen combined with progestogen given for 14 days every 6 months.
- 1 RCT (Rees 2004) compared triphasic (9 days higher dose E only, 12 days E + P, 7 days E lower dose) regimens with biphasic (11 days E only, 10 days E+P, 7 days placebo)

With regard to the outcome of endometrial hyperplasia,after one year of therapy only one RCT found a statistically significant difference between the groups (Scandinavia 1996 (n=240) Figure 34. This study had a planned duration of five years but was stopped after an average of 2.8 years treatment in the long cycle group (moderate dose E + 1mg NETA for 10 days every 3 months) because the rate of endometrial hyperplasia was so unexpectedly high in the first year in this group (7.5%) (OR 8.7 95% CI 1.93 to 39.27). This difference persisted in the second and third years of the trial with 15% endometrial hyperplasia after 3 years of therapy in the long cycle group compared to 2.0% in the monthly sequential group.

Figure 34. Forest plot of comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), outcome: 8.1 Endometrial hyperplasia at 1 year.



Two other small RCTs compared long cycle regimens with monthly sequential regimens (Heikkinen 1997; Williams 1994). Heikkinen 1997 randomised 78 women into 3 groups (monthly cyclic, longcycle and placebo and used high dose estrogen combined with 10 mg MPA for 10 days per month or 14 days per 3 months. Williams 1994 randomised 80 women into 3 groups, with moderate dose estrogen (0.625 mg CEE) plus 10 mg MPA given for 14 days per month, 14 days per 3 months or 28 days per 3 months respectively. There was no statistically significant difference between the groups in the rate of endometrial hyperplasia after 1 year in either study, and the Heikkinen 1997 study found no statistically significant difference between the groups after 2 years. Neither of these trials specified power calculations, but Williams 1994 stated that the study "probably lacked power to find a difference between the groups".

Another RCT (Prestwood 2003 (n=167) compared ultra low dose estrogen (0.25mg 17β E2 daily) plus 100 mg of progesterone for 2 weeks every 6 months, with placebo. One hundred and eight women completed 3 years of therapy and there was no statistically significant difference between the groups in the rate of endometrial hyperplasia.

In the 9 RCTs (Al-Azzawi 2001;Byrjalsen 1999; Chang 2003; Ferenczy 2002; Koninckx 2005; Meuwissen 2001; MSG 1994; PEPI 1995; Scandinavia 1996) that reported the outcome of endometrial cancer there was no statistically significant difference between groups receiving any of the sequential regimens compared, after 1, 2 or 3 years of hormone therapy.

The PEPI 1995 study found no statistically significant difference between groups receiving the sequential regimens in the rate of unscheduled biopsies . There was no statistically significant difference found in the odds of adherence to therapy in the sequential regimens compared in the two RCTs that reported this outcome (PEPI 1995; Rees 2004). Likewise there was no statistically significant difference found in odds of withdrawal due to adverse events in the regimens compared in any of the 5 RCTs that reported this outcome.

Sensitivity analyses

For many of the comparisons, the outcomes were recorded by only one or two trials and sensitivity analysis could not be performed. Sensitivity analysis was conducted for comparisons 1.2.1 and 1.2.2 where unopposed estrogen therapy was compared with placebo and the outcome was endometrial hyperplasia after 2 years of therapy.

- For low dose estrogen alone, the OR for trials with low risk of bias increased to 2.9 (95% CI 1.4 to 6.0) compared to OR 2.6 (95% CI 1.4 to 5.0) when all trials were included.

- For moderate dose estrogen alone the OR increased to 11.5 (95% CI 7.2 to 18.3) for trials with low risk of bias from 10.1 (95% CI 6.5 to 15.7) for all trials.

Funnel Plots

Although funnel plots were planned to investigate possible publication bias, there were so few studies in any of the meta analyses that it was considered that funnel plots were unlikely to have sufficient power to distinguish chance from meaningful asymmetry.

Heterogeneity

Throughout this systematic review there is a high level of clinical heterogeneity due to variations in the populations of women included, for example in age, years since menopause, and the variety of hormone therapy doses and regimens compared. We have attempted to deal with this by separating out the regimens and doses, which has had the undesirable effect of reducing the potential for meta analysis. For example, when unopposed estrogen was compared with continuous estrogen and progesterone there were 13 different regimens used in 6 RCTs. We chose to display each regimen separately, which meant that only 3 of the 13 regimens had more than one trial contributing data.

When continuous E + P was compared with sequential E + P therapy with regard to the outcome 'withdrawal due to adverse events', significant heterogeneity was also evident from the forest plot. We did not calculate a pooled estimate here as only one of the 4 trials was considered to have a low risk of bias.

DISCUSSION

The assessment of endometrial hyperplasia in this review is clinically important because it is associated with an overall increased risk of endometrial cancer, although this risk differs according to the type of hyperplasia diagnosed. There is evidence that untreated simple hyperplasia without atypia progresses infrequently over a 13 year period to carcinoma while the risk of progression to carcinoma is greater in women with complex hyperplasia (Kurman 2000). Untreated hyperplasia with atypia is more likely to progress to cancer (Kurman 2000; Terakawa 1997). Most of the trials included in this review have distinguished 'hyperplastic' endometrium of any type from other types of endometrium.

Unopposed estrogen therapy was associated with a significantly increased risk of endometrial hyperplasia at 2 and 3 years at all doses and there was evidence of a dose-response relationship and a duration of treatment-response relationship between unopposed estrogen and risk of hyperplasia, a result which has been well documented elsewhere (Ziel 1975; Mack 1976; Grady 1995). After one year of treatment, low dose unopposed estrogen was associated with a marginally non significant increase in endometrial hyperplasia compared to placebo (Figure 2).

The addition of progestogen to unopposed estrogen therapy in women with intact uteri significantly reduced the risk of endometrial hyperplasia, when either sequential or continuous combined regimens were adopted. The results confirm that after one year of therapy, continuous combined estrogen plus progestogen at any of the doses used in the trials is associated with a statistically significant reduction in risk of endometrial hyperplasia when compared to unopposed estrogen regimens. After two years of therapy, low dose estrogen plus either 1.5 or 2.5 mg MPA showed a statistically significant reduction in odds of hyperplasia compared to unopposed estrogen, but there was insufficient power to determine the endometrial safety of 1- 5 µg ethinyl estradiol combined with 0.2 to 1 mg NETA.

The review also found that when unopposed estrogen was compared to continuous E + P there was an increased odds of endometrial cancer in the unopposed estrogen group.

There was a statistically significant reduction in the odds of developing endometrial hyperplasia in all the sequential combined estrogen plus progestogen regimens compared with unopposed estrogen therapy. The duration of progestogen in the included studies in this review ranged from 10 to 14 days. Our review confirms the finding that doses of progestogen in sequential therapy need to be given for at least 10 days, as reported by a large case-control study (Pike 1997).

The two studies that reported the outcome of endometrial cancer (MSG 1994; PEPI 1995) showed no difference in odds of developing endometrial cancer between women receiving unopposed estrogen and those receiving sequential 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.

One large trial (WHI 2002) of continuous E+P versus placebo found that the annualised incidence of endometrial cancer in the E+P group was 0.06% compared to 0.07% in the placebo group after a mean 5.6 years of follow up (Figure 12). The risk of endometrial cancer was not significantly different in the two groups but endometrial cancer is an uncommon event and an adequate assessment of this risk is unlikely to be made within the context of the limited time frame of the number of trials included in this review (maximum six years WHI 2002). It should also be noted that if a woman in the WHI trial developed endometrial hyperplasia of any type, hormone therapy was stopped and treatment of hyperplasia undertaken. The low rates of endometrial cancer in both groups show the value of regular monitoring of women taking hormone therapy.

This review is restricted to trials of oral hormone therapy. However it should be noted that intrauterine progestogen-releasing systems are available, and can be used in combination with oral estrogen in hormone therapy. Intrauterine progestogen-releasing systems induce profound endometrial suppression and may overcome many of the problems of sensitivity to systemic progestogens while also offering benefits such as control of heavy menstrual bleeding and contraception in perimenopausal women (Raudaskoski 2002). There is a need for trials to evaluate the benefits and harms of intrauterine progestogen-releasing systems used in combination with low dose oral estrogen for both short and longer term hormone therapy in peri and postmenopausal women.

In the trials that compared continuous combined regimens directly with sequential regimens (comparison 6) there was no statistically significant difference in the odds of endometrial hyperplasia after 1, 2 or 3 years. There was no statistically significant difference in the odds of endometrial cancer after up to three years. However the sequential regimens included in these comparisons were quite varied and there was insufficient data to determine the relative merits of the different types of regimens used. There was no difference with regard to the outcome of adherence, withdrawal due to adverse events, nor in the rate of unscheduled biopsies between the continuous and sequential regimens compared.

The comparisons between the various continuous combined regimens found no 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.

Long (or very long) cycle sequential therapy (progestogen given once every three months) was compared with short cycle sequential therapy (progestogen given once a month) in four trials (Heikkinen 1997; Prestwood 2003; Scandinavia 1996; Williams 1994). In one trial (Scandinavia 1996) where the long cycle group received moderate dose E (2mg 17β estradiol) + 1mg NETA for 10 days every 3 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 to the planned 5 years).

This finding was not repeated in two small studies (Heikkinen 1997; Williams 1994) which found no statistically significant difference between long cycle and short cycle groups in the rate of endometrial hyperplasia after 1 or 2 years of hormone therapy. A further study (Prestwood 2003) which compared placebo with ultra low dose estrogen plus 14 days of progesterone (0.25 mg 17β estradiol +100 mg micronised progesterone) given every six months (very long cycle), showed no statistically significant difference between the groups with regard to endometrial hyperplasia after 3 years of therapy.

The PEPI 1995 study found a marginally statistically significant difference in the rate of endometrial hyperplasia at 2 years between women receiving sequential therapy and those receiving placebo, but this is unlikely to be clinically significant. After 3 years of

treatment there was no statistically significant difference between these groups.

Adherence to therapy and the acceptability of therapy regimens to women are estimated and interpreted differently in the trials included in this review. We have chosen to define adherence to therapy as occurring when women take more than 80% of prescribed hormone doses as measured by counts of remaining tablets at clinic visits. Only one RCT (PEPI 1995) compared unopposed estrogen with combined regimens and reported adherence to therapy. Adherence was greater in both continuous and sequentially combined regimens than in unopposed estrogen regimens.

One of the strengths of this review is the grouping of a number of different estrogenic preparations together with approximately similar endometrial effects. A further outcome of this review is a list of minimum progestogen doses which have been found to safely 'oppose' these estrogen doses with regard to preventing the development of endometrial hyperplasia. (see Table 2; Table 4; Table 3; Table 5)

Both withdrawals due 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.

AUTHORS' CONCLUSIONS

Implications for practice

- The evidence that unopposed estrogen therapy increases the risk of endometrial hyperplasia shows a consistent association between the level of risk and the duration and strength of the dose. As low dose unopposed estrogen was associated an increase in the risk of endometrial hyperplasia over placebo at 1 year duration that bordered on statistical significance, clinicians utilising this dose for this short time frame should monitor the endometrial thickness by ultrasound. Best practice is to use both estrogen and progestogen in women with a uterus. There was no evidence of an increase in endometrial hyperplasia at 3 years associated with ultra low dose estrogen (0.25 mg 17βE2) (Prestwood 2003) and progesterone for 15 days every 6 months. However there were no data to support that ultra low dose oral 17βE2 would be adequate for symptom relief, as the primary outcome in this study was bone protection.

- Low dose ethinyl estradiol (5 micrograms) required 1mg NETA continuously to protect the endometrium (CHART 1996; Portman 2003). Ethinyl estradiol, commonly used in the oral contraceptive pill, has a pronounced effect on hepatic metabolism, and is now rarely used for hormone in postmenopausal women.

- Recent advice regarding hormone therapy for women with troublesome menopausal symptoms is to use the lowest effective dose and determine the duration of therapy based on an estimation of the benefits and harms for each individual woman. The use of hormone therapy should be reviewed by the woman with her doctor, as menopausal symptoms often resolve within a year of the onset of the menopause (Hickey 2005). For many women low dose hormone gives adequate relief of symptoms (Peeyananjarassri 2005). However at the time of writing not all countries have packaged low dose sequential and combined continuous regimens generally available. In this situation clinicians will need to separately prescribe the progestogen in doses that give endometrial protection.

- The combined continuous regimen is suitable for women who are more than one to two years postmenopausal; use for women in early menopause can lead to unacceptable bleeding patterns (Archer 1999)

- Low dose combined continuous regimens currently manufactured include 1mg 17βE2 combined with 1mg NETA daily and 1mg estradiol valerate combined with 2mg of drospirinone daily. This systematic review has shown that 1.5mg of MPA given continuously with 0.3 mg of CEE will give endometrial protection (Table 4). However because this particular dose of MPA is not currently manufactured, clinicians will need to prescribe the 2.5mg MPA tablet as this is the minimum dose available. For 17βE2 this systematic review shows that 0.1 mg of NETA taken continuously will give endometrial protection (Table 2). However the commonly available product is currently one progestogen-only pill containing 0.35mg norethisterone.

- Sequential regimens are suitable for women in early menopause. The RCTs included in this review with sequential regimens using low dose estrogen use regimens with types and doses of progestogens not commonly available as separate tablets (Table 5). This makes separate prescribing of low dose sequential hormone therapy problematic. A low dose sequential product containing 1 mg 17βE2 together with 10 days of 1mg NETA is manufactured, but may not be available in all countries.

Implications for research

Many of the studies in this review are small and lack statistical power, and others recruited larger numbers of women but high rates of attrition for various reasons resulted in small numbers of women having endometrial biopsies after 2 or 3 years of treatment. Larger studies, examining the endometrial safety of short term use (</= 1 year) of unopposed low dose estrogen would help to determine the safety of this regimen.

Data are also lacking regarding endometrial safety with sequential regimens containing low doses of estrogen with the more commonly available progestogens, which would be the treatment of choice for perimenopausal women. Results from such studies would aid clinicians who wish to individually prescribe low dose hormone combinations in countries where these packaged regimens are not available. There is also a need for trials to evaluate the benefits and harms of intrauterine progestogen-releasing systems used in combination with low dose oral estrogen for both short and longer term hormone therapy in peri and postmenopausal women.

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Contributors to previous published versions of this review include Jane Suckling (past reviewer), who updated the review in 2004. She performed searches, selected trials for inclusion, assessed quality, performed data extraction, entered data, and prepared the final review.

Anne Lethaby who selected trials for inclusion, assessed quality, performed data extraction, entered data, prepared the final review and incorporated suggested changes.

Cindy Farquhar reviewed the protocol, performed data extraction and commented on the final draft of the review.

Helen Roberts assessed included trials for quality, performed data extraction and commented on the final draft of the review.

Arpine Sarkis (past reviewer) registered the title, prepared the protocol, selected trials for inclusion, assessed quality and performed data extraction for the first published version of this review. Ruth Jepson reviewed the protocol, performed searches, selected trials for inclusion, assessed quality, and commented on the final draft of the review in 1999. David Barlow provided comment on the protocol and the final draft of the review in 1999.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

AinMelk 1996

Methods	Randomisation: random number table Open label single centre, parallel group trial Number of women randomised: 59 Number of women analysed: 53 Number of withdrawals: 6 (2 in gp1 due to mastalgia, nausea and bleeding and 2 from each group due to bleeding) Power calculation and intention to treat analysis not described Sources of funding: Upjohn (Canada), Wyeth-Ayerst (Canada) and Ogen provided medication for the study
Participants	Country: Canada Inclusion criteria: healthy postmenopausal at least one year post natural menopause, with intact uterus, vasomotor symptoms and normal endometrial histology Exclusion criteria: Previous use of HT
Interventions	Continuous (1) 0.625 mg conjugated equine estrogens (CEE) + 2.5 mg medroxyprogesterone acetate (MPA) (2) 0.625 mg estrone sulphate + 2.5 mg medroxyprogesterone acetate (MPA) Duration: 2 years (104 weeks)
Outcomes	Irregular bleeding, endometrial histology, Amenorrhoea
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	Yes	Reasons for withdrawal described
Free of selective reporting?	Unclear	Mammography and Pap smears planned but not reported
Free of other bias?	Yes	2 parallel groups, balanced at baseline

Al-Azzawi 2001

Methods	Randomisation: method not stated. Randomised double blind multicentre study (n=42) Number of women randomised: 487 Number of women analysed: 349 Number of withdrawals: 138 of which 64% were due to adverse events (specified) not including bleeding Source of funding: Joint development programme by Aventis and Wyeth-Ayerst International
Participants	Country: not specified - Europe & United Kingdom Inclusion criteria: Postmenopausal women with intact uterus, at least 6 months of amenorrhoea or at least 12 months on HT, FSH, LH & E2 levels in the post menopausal range, and at least 3 hot flushes per day. There was a washout period of 4 weeks for those previously on HT Exclusion criteria: specified intercurrent disease, any contraindication to hormone therapy, endometrial hyperplasia
Interventions	Continuous versus sequential (1) 2 mg E2 + 0.25 mg trimegestone daily (2) 2 mg E2 + 0.5 mg trimegestone daily (3) 2 mg E2 daily for 12 days, then 2 mg E2 + 1 mg norethisterone daily for 10 days, then 1 mg E2 daily for 6 days Duration: 13 cycles
Outcomes	mean duration of withdrawal bleeding, severity of endometrial bleeding, endometrial hyperplasia, endometrial cancer
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind with treatments placed into capsules of identical appearance
Incomplete outcome data addressed? All outcomes	Unclear	Reasons for early withdrawal described in table 4 for the 28% of women who did not complete the study
Free of selective reporting?	Yes	all planned outcomes reported
Free of other bias?	Yes	3 parallel groups, some difference between groups in menopause duration

Archer 2005

Methods	Randomisation; method not stated, Multicentre, double blind, parallel group study Number of women randomised: 1147 Number of women analysed:1142 Source of funding:Berlex Inc,New Jersey
Participants	Country:USA women recruited from several centres Inclusion:post menopausal women,aged 42-75, with 6-12 months amenorrhoea, with intact uterus, with or without menopausal symptoms.Negative endometrial biopsy or endometrial thickness <5mm. Serum FSH >50 IU/L, serum E2 <20 pg/ml Exclusion: Abnormal endometrial histology, Specified intercurrent illness
Interventions	Continuous (1) E2 1mg daily (2) E2 1mg plus 0.5 mg drospirinone (DRSP) daily (3) E2 1mg plus 1 mg drospirinone (DRSP) daily (4) E2 1mg plus 2 mg drospirinone (DRSP) daily (5) E2 1mg plus 3 mg drospirinone (DRSP) daily Duration: 1 year
Outcomes	Endometrial hyperplasia, bleeding patterns
Notes	hot flush frequency, urogenital symptoms, Quality of life

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Participants, medical staff and outcome assessors were blinded to treatment allocation
Incomplete outcome data addressed? All outcomes	Unclear	5 women who were randomised did not take any of the medication. Paper describes ITT analysis on 1142 women who took at least one dose of the study medication. 297 (26%) of those randomised prematurely discontinued the study medication for reasons described in table 1. However endometrial biopsy results are only available for the 966 (86%) of participants who underwent both a baseline and a post baseline biopsy
Free of selective reporting?	Yes	Planned outcomes reported
Free of other bias?	Yes	5 parallel groups, well balanced at baseline

Bouchard 2005

Methods	Randomisation: method not stated double blind, multicentre (107 sites in 13 countries) randomised trial by the Trimegestone 301 study group Number of women randomised:911 Number of women analysed:?? Number of withdrawals: approx 167 women withdrew due to adverse events (74 from gp 1, 56 from gp2 and 37 from gp 3)
Participants	Countries: Israel, Denmark, Estonia, Finland, France, Germany, Italy, Latvia, Norwary, Spain, Sweden, the Netherlands, United Kingdom Inclusion criteria:Healthy postmenopausal women with an intact uterus, more than 3 hot flushes per day, at least 6 months amenorrhoea or 12 months previous HT, BMI less than 35 Exclusion criteria:Intercurrent illness (specified), endometrial hyperplasia, contraindication to hormone therapy
Interventions	Continuous (1) 1 mg 17 β estradiol (E2) +0.125 mg trimegestone (TMG) (2) 2 mg 17 β estradiol (E2) +1 mg norethisterone acetate (NETA) (3) 1 mg 17 β estradiol (E2) + 0.5 mg norethisterone acetate (NETA) Duration: 2 years
Outcomes	amenorrhoea, mean number of bleeding/spotting days, endometrial hyperplasia
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	Unclear	Numbers randomised to each part of the study unclear
Free of selective reporting?	Yes	Planned outcomes reported
Free of other bias?	Unclear	At baseline some differences between groups in smoking status, and duration of menopause which were accounted for in the analysis

Bruhat 2001

Methods	Randomisation:method not stated Design: Multicentre (15 in France and 18 in Germany), open label parallel group Number of women randomised:427 Number of women analysed:340 Number of withdrawals:87 (20%) mostly due to adverse events incl bleeding (15,10,3 women in gps A,B & C resp), weight gain (7,3,1 respectively) mastalgia (12, 6, 5 respectively) Source of funding:not stated
Participants	Countries:France and Germany Inclusion criteria: healthy post menopausal women aged 45-65 years, at least 3 years past menopause, with BMI less than or equal to 31, intact uterus and normal gynaecological findings. Women on HT had a 1 month washout period. Exclusion criteria:Endometrial hyperplasia, specified serious intercurrent illness
Interventions	Continuous (1) 1mg E2V + 2.5mg MPA daily for 6 months, then 2mg E2V +2.5mg MPA daily (2) 1mg E2V + 5mg MPA daily for 6 months, then 2mg E2V +5mg MPA daily (3) 2mg E2V + 1mg NETA daily Duration: 12 months
Outcomes	Mean number of bleeding days per cycle at 1 yr, Climacteric symptoms, lipid profile, endometrial hyperplasia, withdrawal due to adverse events, adherence to protocol
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	Unclear	all the women who withdrew from the study (20% of those randomised) are accounted for but there is no indication of how many women had endometrial biopsy taken at study completion
Free of selective reporting?	Unclear	Reasons for participants discontinuation in study not clearly reported
Free of other bias?	Yes	Three groups balanced at baseline

Byrjalsen 1992

Methods	Randomisation method not stated. Single blind, parallel group, placebo controlled, single centre, Number of women randomised:73 Number of women analysed:66 Number of early withdrawals: 7 (3 due to vaginal bleeding, 1 due to oedema of the legs, 2 due to lack of time, 1 due to illness unrelated to study)
Participants	Country: Denmark Inclusion criteria:healthy post menopausal women aged 45-54 years who had experience natural menopause 9-40 months previously. Exclusion criteria: diseases or concomitant medications known to influence study measurements
Interventions	sequential vs sequential vs placebo (A) 2mg E2V days 1-21 + 10mg MPA daily days 12-21 (B) 1.5mg 17β E2 days 1-24 + 150µg desogestrel days 13-24 (C) placebo Duration 2 years
Outcomes	Mean duration of withdrawal bleed, amenorrhoea, endometrial biopsy
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Single blind
Incomplete outcome data addressed? All outcomes	Yes	73 women were randomised to 3 groups. Biopsies at the end of the study on 56 women (77% of those randomised)
Free of selective reporting?	Yes	planned outcomes reported
Free of other bias?	Yes	3 groups balanced at baseline

Byrjalsen 1999

Methods	Randomisation method not stated (randomisation mentioned in the conference paper but not in the full paper) Double blind, single centre, parallel groups Number of women included: 278 Number of women analysed: 168 Number of withdrawals: 110 (42 due to uterine bleeding, 34 due to medical adverse events, 35 due to events unrelated to the trial)
Participants	Country:Denmark Inclusion criteria:healthy post menopausal women aged 45-63 years who had undergone a natural menopause Exclusion criteria: intercurrent diseases, or concomitant medications known to influence study measurements
Interventions	sequential versus continuous vs placebo (A) 2mg 17β E2 daily days 1-28 + 50 µg gestodene daily on days 17-28 (B) 2mg 17β E2 daily days 1-28 + 25 µg gestodene daily on days 17-28 (C) 1mg 17β E2 daily days 1-28 + 25 µg gestodene daily on days 17-28 (D) 1mg 17β E2 + 25 µg gestodene daily (continuous) (E) placebo Duration: 2 years
Outcomes	Endometrial biopsy at 2 years, bleeding patterns, compliance
Notes	Numbers allocated to each group calculated from tables 1 & 2

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind - investigators and participants
Incomplete outcome data addressed? All outcomes	Unclear	110 of the 278 women randomised (40%) withdrew before the end of the study
Free of selective reporting?	Unclear	planned outcomes reported. Reasons for early withdrawal given. 2 year biopsies on 46% of those randomised - paper states that pretreatment data of withdrawals are similar to completers
Free of other bias?	Unclear	five groups, not told how many randomised to each group, but baseline data only given for completers (46% of those randomised)

Byrjalsen 2000

Methods	Randomisation using random numbers. 2 groups double blind and comparison group single blind, parallel group, single centre,allocation concealed during the study. No women randomised: 200 No women analysed: 113 Reasons for withdrawal Gp A uterine bleeding (11) AE of medication (3) reasons unrelated to treatment (9) lost to follow up(1) total 24 Gp B AE of medication (7) reasons unrelated to treatment (8) total 15 Gp C uterine bleeding (5) AE of medication (6) reasons unrelated to treatment (7) lost to follow up (1) total 19 Gp D AE of the medication (3) reasons unrelated to treatment (15) lost to follow up (2) total 20
Participants	Country:Denmark Inclusion criteria: healthy post menopausal women aged 45-65 who had undergone natural menopause at least one year before the study. Exclusion criteria: Diseases or medication known to influence study measurements. Endometrial dysplasia or malignancy
Interventions	intermittent vs continuous vs placebo (A) 1.5mg piperazine oestrone sulphate (POS) daily + 0.7mg norethisterone on days 4-6, 10-12, 16-18, 22-24, 28-30 (high EP group) (B) 0.75mg POS daily + 0.35mg norethisterone on days 4-6, 10-12, 16-18, 22-24, 28-30 (low EP group) (C) 2mg 17β E2 + 1mg norethisterone daily (continuous combination) (D) Placebo
Outcomes	After 2 years of treatment blood samples, endometrial thickness and endometrial biopsy
Notes	Part of this study is described as double blind and part as single blind. 3 groups had medication identical in appearance (high EP, low EP and placebo), while the continuous combined group had medication that looked different

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Unclear	High EP and Low EP sequential groups were double blinded (investigator and participant) . The continuous EP and placebo groups were described as single blinded
Incomplete outcome data addressed? All outcomes	Unclear	78 women (39%) withdrew from the study prematurely, 9 refused a biopsy, 20 biopsies yielded insufficient tissue and 2 biopsy samples were lost. Endometrial hyperplasia

Byrjalsen 2000 (*Continued*)

		data is from the remaining 91 participants (46% of those randomised)
Free of selective reporting?	Yes	planned outcomes reported and early withdrawals well desribed
Free of other bias?	Yes	4 parallel groups balanced at baseline for the parameters reported

Chang 2003

Methods	Randomisation method not stated. Groups are of uneven size 142, 84, 88 Single centre, double blind No women randomised:314 No women analysed: varied between 81 and 241 (102, 66, 73) No withdrawals: 73 due to intolerable breast tenderness or loss to follow up Source of funding: grant from National Sciences Council, Taiwan
Participants	Country: Taiwan Inclusion criteria: Postmenopausal women with intact uterus, aged 45-65, referred to the Menopausal Special Clinic at National Taiwan University Hospital, Taipei. Women were amenorrhoeic for at least 1 year or 6 months plus serum FSH >40 IU/L and estradiol <20 ng/l Exclusion criteria: history of endometrial or breast cancer
Interventions	sequential (A) 0.625mg CEE daily days 1-25 + 5mg MPA daily on days 12 - 25 (B) 0.625mg CEE daily days 1-25 + 10mg MPA daily on days 12-25 (C) 0.625mg CEE daily days 1-25 + 20mg dydrogestone daily on days 12-25 Duration: 1 year
Outcomes	endometrial thickness, endometrial biopsy
Notes	Approximately 30% of participants had 'concomitant diseases' including diabetes and hypertension

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	Unclear	23% of those randomised withdrew due to "intolerable breast tenderness and loss to follow up". Numbers of withdrawals in

Chang 2003 (*Continued*)

		each group not given
Free of selective reporting?	Unclear	planned outcomes reported, numbers of participants withdrawing early not described
Free of other bias?	Yes	3 groups well balanced at baseline

CHART 1996

Methods	Randomised, double blind, placebo controlled, multicentre study. Method of randomisation and allocation concealment: randomisation code prepared by Biometrics Department in blocks of 9 with computer generated random numbers. Number of women randomised: n = 1265 Number of withdrawals: n = 570 (at 2 years) based on losses to follow up and stopping rule. Excluding the 10 mcg EE2 group (treatment terminated due to high incidence of endometrial hyperplasia), 73% of subjects completed the study. Source of funding: Parke-Davis Pharmaceutical Research.
Participants	Country: USA (65 study centres participated). Participants: women aged 40 years or older who had undergone spontaneous menopause within the last five years and who had an intact uterus. Inclusion criteria: Healthy volunteers; FSH greater or equal to 40 IU/L; estradiol less than or equal to 73 pmol/L; atrophic endometrium; no major illnesses. Exclusion criteria: Baseline vaginal bleeding; baseline mammography suggestive of malignant disease; chronic use of medications that affect bone calcium metabolism or significant vasomotor symptoms that required medical treatment. No participant was to have taken oral or transdermal estrogen therapy for 6 months prior to randomisation
Interventions	continuous vs placebo (1) 1 mcg daily of oral ethinyl estradiol (EE2) plus 0.2 mg of oral norethindrone acetate (NA) continuously (2) 2.5 mcg daily of oral ethinyl estradiol (EE2) plus 0.5 mg of oral norethindrone acetate (NA) continuously (3) 5 mcg daily of oral ethinyl estradiol (EE2) plus 1 mg of oral norethindrone acetate (NA) continuously (4) 10 mcg daily of oral ethinyl estradiol (EE2) plus 1 mg of oral norethindrone acetate (NA) continuously (5) 1 mcg daily of oral ethinyl estradiol (EE2) continuously (6) 2.5 mcg daily of oral ethinyl estradiol (EE2) continuously (7) 5 mcg daily of oral ethinyl estradiol (EE2) continuously (8) 10 mcg daily of oral ethinyl estradiol (EE2) continuously (9) Control group: placebo Duration: 2 years
Outcomes	Endometrial biopsy at baseline and after 6,12,18 and 24 months of therapy

CHART 1996 (*Continued*)

Notes	Based on priori stopping rules, subjects in Group 8 (10 mcg daily of oral ethinyl estradiol (EE2) continuously) were terminated from the study early owing to a high rate of hyperplasia for that treatment group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	(A) randomisation code prepared by Biometrics Department in blocks of 9 with computer generated random numbers
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	Yes	subjects in the 10mg EE group were terminated early. all the other groups had similar rates of withdrawal ranging between 22-30%
Free of selective reporting?	Unclear	planned outcomes reported but reasons and numbers of withdrawals not described
Free of other bias?	Yes	9 parallel treatment groups well balanced at baseline

Corson 1999

Methods	Randomisation method not stated. Multi-centre, parallel group design with double blinding. Number of women randomised: n = 1253 Number of women analysed: n = 903 Number of withdrawals: n = 361 (E2 1 mg; 100 women, E2/NGM 30 mcg 65 women, E2 1 mg/NGM 90 mcg 97 women, E2 1 mg/NGM 180 mcg 99 women. Reasons for early withdrawal provided in Table 2 Source of funding:not stated
Participants	Country: USA Age: 40-65 years Inclusion criteria: Postmenopausal for > 12 months, serum estradiol <20 pg/ml and serum FSH > 30 mlU/ml, intact uterus, no HT in the 8 weeks before study entry, discontinue injectable or implantable sex steroids use 6 months before study entry, have no contra-indications to estrogen and /or progestin therapy
Interventions	intermittent vs unopposed E (1) 1mg 17β estradiol (E2) for 3 days, then 1 mg E2 + norgestimate (NGM) 30 mcg for 3 days (sequential)

Corson 1999 (*Continued*)

	(2) 1 mg E2 for 3 days, then 1 mg E2 and 90 mcg NGM for 3 days (sequential) (3) 1 mg E2 for 3 days, then 1 mg E2 and 180 mcg NGM for 3 days (sequential) (4) Estrogen only group, 1 mg E2 daily (continuous) Duration: 12 months
Outcomes	Endometrial hyperplasia
Notes	Author contacted regarding randomisation method and exclusion criteria

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	361 women of the 1253 randomised (29%) withdrew from the study, but analysis is by ITT
Free of selective reporting?	Yes	planned outcomes and reasons for early withdrawal from study well described
Free of other bias?	Yes	4 parallel treatment groups well balanced at baseline

Ettinger 1992

Methods	Randomisation method not stated. Single centre, parallel group dose-ranging design with double blinding in Phase 1 Number of women randomised: 63 (n = 52 with intact uterus). Number of women analysed for endometrial outcome n = 28 Source of funding: Mead Johnson Laboratories, Division of Bristol Myers
Participants	Country: USA Postmenopausal mostly white women, aged 40 to 58 years, recruited from advertisements and physician referrals. Inclusion criteria: Within 5 years of menopause (confirmed by bilateral oophorectomy or no menses for >= 6 months; estrogen deficiency (confirmed by FSH>40 U/L); body weight within 20% of ideal for height (Metropolitan Life Company Tables). Exclusion criteria: Presence of diseases/conditions known to affect skeletal health such as thyroid/parathyroid disorders or other disorders of calcium homeostasis; use of anti-convulsants or glucocorticoids; evidence of renal, hepatic, cardiac or malignant diseases
Interventions	Unopposed E vs placebo (1) 0.5 mg micronized 17β-estradiol + calcium carbonate supplements daily on 23 of

Ettinger 1992 (*Continued*)

	28 days. (2) 1.0 mg micronized 17β-estradiol + calcium carbonate supplements daily on 23 of 28 days (3) 2.0 mg micronized 17β-estradiol + calcium carbonate supplements daily on 23 of 28 days (4) Control: Placebo + calcium carbonate supplements daily on 23 of 28 days Duration: 18 months
Outcomes	Frequency of hyperplasia (from endometrial biopsy) Frequency of unexpected bleeding
Notes	Eleven women (17.5%) had previous hysterectomy so above outcomes analysed in a subgroup of 52 women. Primary objective of the study was to evaluate bone loss

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Phase 1 double blind (18 months)
Incomplete outcome data addressed? All outcomes	Unclear	28 women (54%) of those randomised had an endometrial biopsy at the end of the treatment
Free of selective reporting?	Yes	planned outcomes and numbers and reasons for early withdrawal described
Free of other bias?	No	small study with 4 parallel groups not well balanced at baseline

Ferenczy 2002

Methods	Randomisation method not stated. Multicentre, double-blind placebo controlled study. Number of women randomised: n = 595 Number of women analysed: n = 579 Number of withdrawals: n = 152 Source of funding: Solvay pharmaceutical.
Participants	Non-hysterectomized, postmenopausal women with amenorrhoea of at least 6 months or surgically post-menopausal(following bilateral oophorectomy without hysterectomy, more than 3 months prior to enrolment), FSH within normal postmenopausal range. Age: 45-65 years from Quebec, Canada, Netherlands. Exclusion criteria: abnormal (uninvestigated bleeding) vaginal bleeding, the use of estrogens and or progestogens and or androgens in the proceeding 6 months or more and

Ferenczy 2002 (*Continued*)

	any previous use of estradiol pellet/implant therapy
Interventions	sequential vs placebo (1) placebo (2) 1mg/day 17β estradiol/5 mg dydrogesterone for the last 14 days of each 28 day cycle (3) 1 mg/day 17β estradiol/10 mg dydrogesterone for the last 14 days of each 28 day cycle (4) 2 mg/day 17β estradiol/10 mg dydrogesterone for the last 14 days of each 28 day cycle (5) 2 mg/day 17β estradiol/20 mg dydrogesterone the last 14 days of each 28 day cycle Duration: 26 cycles (104 weeks)
Outcomes	Endometrial hyperplasia, Endometrial cancer
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	442 women (74%) of the 595 randomised had an endometrial biopsy at the end of the treatment
Free of selective reporting?	Yes	planned outcomes and numbers and reasons for early withdrawal reported
Free of other bias?	Yes	5 parallel groups well balanced at baseline

Gelfand 1989

Methods	Computerised random assignment controlled by pharmacist. Single centre, parallel group design, double blinding. Number of women randomised: n = 173 Number of withdrawals: n = 78 (n = 24: 1 year of treatment not complete when study terminated and not included in analysis; n = 54: withdrew during the study for medical reasons but withdrawals not comparable between treatment groups (9.5%, 9%, 2% and 28% respectively)) Source of funding: Ayerst, McKenna and Harrison
Participants	Country: Quebec, Canada, Netherlands Age: 45-65 years Non-hysterectomized, postmenopausal women with amenorrhoea of at least 6 months

Gelfand 1989 (*Continued*)

	or surgically post-menopausal (following bilateral oophorectomy without hysterectomy, more than 3 months prior to enrolment), FSH within normal postmenopausal range. Exclusion criteria: abnormal (uninvestigated bleeding) vaginal bleeding, the use of estrogens and or progestogens and or androgens in the proceeding 6 months or more and any previous use of estradiol pellet/implant therapy
Interventions	Unopposed E vs sequential (1) 0.625 mg daily of oral conjugated equine estrogen (CEE) for 25 days of a 30 day cycle, plus placebo (2) 0.625 mg daily of oral conjugated equine estrogen (CEE) for 25 days of a 30 day cycle, plus 5 mg oral medroxyprogesterone acetate added to the last 11 days of the CEE cycle (3) 1.25 mg daily of oral conjugated equine estrogen (CEE) for 25 days of a 30 day cycle, plus placebo (4) 1.25 mg daily of oral conjugated equine estrogen (CEE) for 25 days of a 30 day cycle, plus 5 mg oral medroxyprogesterone added to the last 11 days of the CEE cycle Duration: 1 year
Outcomes	Frequency of hyperplasia (endometrial biopsy at baseline, six and twelve months). Withdrawal due to adverse events
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Unclear	95 women of 173 randomised (55%) had endometrial biopsies at the end of the treatment
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawal described
Free of other bias?	Unclear	4 groups with some imbalance at baseline in % smokers and alcohol consumption

Graser 2000

Methods	Randomisation: Method not stated Double blind, multicentre international trial (49 centres in Europe and South Africa) Number of women randomised: 595 Number of women analysed: 410 - 595 Number of withdrawals: 58,67,60 women withdrew from groups 1,2 &3 respectively Source of Funding: Jenapharm GmbH & Co, and Schering AG, Germany
Participants	Countries: Germany. Czech Republic, Poland, Hungary, Bulgaria, South Africa Inclusion criteria: Postmenopausal women with troublesome vasomotor symptoms, aged less than or equal to 65. Other criteria - BMI 20 - 32, >/= 24 months amenorrhoea, serum estradiol in postmenopausal range, serum FSH>/= 30 IU/L Exclusion criteria: Previous HT use (sequential regimen within 4 weeks or continuous regimen within 6 months of start of trial) other treatment for hot flushes, previous or existing serious illness 9specified), endometrial hyperplasia, contraindications to hormone therapy, concomitant medications (specified)
Interventions	continuous (1) 2 mg estradiol valerate + 2 mg Dienogest daily "Climodien" (2) 2 mg estradiol valerate + 3 mg Dienogest daily (3) 2 mg estradiol + 1 mg estriol + 1 mg norethisterone acetate daily "Kliogest" first generation formula Duration:1 year
Outcomes	Vaginal bleeding, endometrial biopsy, adverse events
Notes	Efficacy, vasomotor symptoms, vaginal cytology,

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	396 women of the 595 randomised (67%) had endometrial biopsies at the end of treatment
Free of selective reporting?	Unclear	planned outcomes reported but numbers and reasons for early withdrawals not clearly described
Free of other bias?	Yes	3 parallel groups well balanced at baseline

Greenwald 2005

Methods	Randomisation: method not stated Multicentre (17 sites) double blind, parallel group study Number of women randomised: 327 Number of women analysed: 189 Number of withdrawals: 138 of which 65 were due to adverse events (not specified) Source of funding: grant from Novo Nordisk A/S, Bagsvaerd, Denmark
Participants	Country: United States of America Inclusion criteria: healthy women at least 45 years old, between 1 and 5 years post menopause, with an intact uterus, serum e2 less than 20 pg/ml, and normal BMD Exclusion criteria: serious intercurrent disease (specified) bone disease, immobilisation, treatment with fluoride, calcitonin, bisphosphonate, corticosteroids
Interventions	Unopposed E vs continuous vs placebo (A) placebo (B) 0.25 mg Estradiol (E2) daily (C) 0.5 mg Estradiol (E2) daily (D) 1mg Estradiol (E2) daily (E) 1 mg Estradiol (E2) + 0.25 mg norethisterone acetate (NETA) daily (F) 1 mg Estradiol (E2) + 0.5 mg norethisterone acetate (NETA) daily (G) 2 mg Estradiol (E2) + 1 mg norethisterone acetate (NETA) daily Duration: 26 months
Outcomes	Bone mineral density, Endometrial hyperplasia
Notes	Bone mineral density primary outcome

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	Unclear	Unclear how many women had endometrial biopsies at the end of the treatment period. 138 of the 327 women randomised (42%) withdrew and had last observation carried forward
Free of selective reporting?	Yes	planned outcomes and numbers and reasons for early withdrawal well described
Free of other bias?	Yes	7 parallel groups well balanced at baseline

Harris 1991

Methods	Randomisation method not reported but study medication identical and concealed in identical bottles. Multicentre (3 study sites), parallel group design, placebo controlled with double blinding. Number of women randomised: n = 156. Number of withdrawals: n = 36 (28 lacked TBD values, 2 did not comply and 6 had baseline measurements outside the time limits specified). Power calculation for sample size performed and analysis by intention to treat for the outcomes reported in this review. Source of funding: Not reported.
Participants	Country: USA Postmenopausal women with mean age 51 years recruited from 3 study sites. Inclusion criteria: no use of sex hormones for previous 3 months; last normal period or bilateral oophorectomy for benign conditions >2 months previously; FSH levels within the postmenopausal range; no contraindications to estrogen therapy; no drug treatment (except sex steroids or calcium) for osteoporosis <1 year before entry into the study; resting supine BP <=160/90 mm Hg at first visit; weight within 125% of upper limit of Metropolitan Insurance Company reference weights; spinal bone mineral content measured by tomography >=80 mg/cm3 at first study visit. Exclusion criteria: diseases or conditions that might affect bone or calcium metabolism or gastrointestinal absorption; requirement for medication that might interfere with estrogen metabolism or efficacy or calcium or bone metabolism; treatment with hypolipidaemic agents or ketoconazole; use of fluoride for osteoporosis at any time
Interventions	Unopposed E vs placebo (1) Oestrone sulphate 0.3 mg + 2.5 g calcium carbonate daily for 25 days, followed by 6 days without treatment (2) Oestrone sulphate 0.625 mg + 2.5 g calcium carbonate daily for 25 days + 6 days with no treatment (3) Oestrone sulphate 1.25 mg + 2.5 g calcium carbonate daily for 25 days + 6 days with no treatment (4) Control: Placebo with same regimen Duration: 2 years
Outcomes	Withdrawal due to adverse events, endometrial hyperplasia, non-adherence to therapy
Notes	Primary outcome osteoporosis prevention. Author contacted for clarification of data relating to adherence to therapy and reviewer was referred to Abbott Laboratories. Abbott Laboratories have not replied so adherence to therapy is not included in the review

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	double blind

Harris 1991 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	36 women of the 156 randomised (23%) withdrew prior to the end of the study but endometrial biopsy data available on 98% of those randomised
Free of selective reporting?	Unclear	planned outcomes reported but unsure whether women excluded from analysis were similar to those included
Free of other bias?	Unclear	4 parallel groups with some imbalance in duration of menopause

Heikkinen 1997

Methods	Randomisation method not stated. Single centre, parallel group, blinding unclear. Number of women randomised: n = 78. Number of withdrawals:n=9 Number of women excluded: n = 2. Source of funding: Orion Corporation.
Participants	Country: Finland 78 healthy women, aged 49 to 55, in early menopause recruited from the city of Oulu in Finland. Inclusion criteria: 0.5-3 years postmenopausal (confirmed by FSH), without previous HT, without contraindications for HT. Exclusion criteria: specified diseases.
Interventions	monthly sequential vs long cycle sequential vs placebo (1) 2 mg estradiol valerate on days 1-11 and 2 mg estradiol valerate + 10 mg MPA then placebo for 7 days (2) 2 mg EV on days 1-70 and 2 mg EV + 20 mg MPA on days 71-84 then 7 days placebo (3) Control: Placebo for 24 months Duration: 2 years
Outcomes	Hyperplasia at 2 years Irregular bleeding (data not published) Withdrawal due to adverse events
Notes	Published trial supplied by drug company, Orion Corporation, which manufactures Tridestra, a long cycle sequential O + P treatment. The primary outcomes of this study were effects of HT and exercise on bone density, muscle strength and lipid metabolism. Hyperplasia and adherence to treatment were secondary outcomes
Risk of bias	

Heikkinen 1997 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Incomplete outcome data addressed? All outcomes	Yes	At the end of treatment endometrial biopsies performed on 69 of the 78 women randomised (88%)
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawal well described
Free of other bias?	Yes	3 parallel groups well balanced at baseline

Heikkinen 2000

Methods	Randomisation: method not stated, single centre, parallel groups, described as double blind but 2 of the 6 groups had dose escalation after 6 months Number of women randomised: 419 Number of women analysed: 419 at 2 years, 296 at 4 years, Number withdrawals: 56 at 12 months mainly due to bleeding disturbances Source of funding: not stated
Participants	Country: Oulu, northern Finland Inclusion Criteria: healthy postmenopausal women at least 3 years post last menstruation, with intact uterus and BMI less than or equal to 30. Exclusion criteria: contraindications to hormone therapy, serious intercurrent disease, smoker of more that 15 cigarettes per day, suspected alcohol abuse. 1 month washout period for previous HT users
Interventions	continuous (1)1 -2 mg estradiol valerate (E2V) + 2.5 mg medroxyprogesterone acetate (MPA) daily (2)1 -2 mg estradiol valerate (E2V) + 5 mg medroxyprogesterone acetate (MPA) daily (3)2 mg estradiol valerate (E2V) + 2.5 mg medroxyprogesterone acetate (MPA) daily (4)2 mg estradiol valerate (E2V) + 5 mg medroxyprogesterone acetate (MPA) daily (5)1 mg estradiol valerate (E2V) + 2.5 mg medroxyprogesterone acetate (MPA) daily (6)1 mg estradiol valerate (E2V) + 5 mg medroxyprogesterone acetate (MPA) daily Duration:24 months
Outcomes	bone mineral density,bleeding patterns, endometrial hyperplasia
Notes	This study was a randomised comparison for the first 7 years, and outcomes from this period are included in this review. After 7 years the women in groups 1&3 stopped treatment because this HT regimen was no longer available. 198 of 279 women originally in the other groups were able to continue on 2/5, 1/2.5 or 1/5 doses of E2V/MPA for a further 18months and then all were given 1/2.5 for 6 months and then followed for a further year after HT was stopped

Risk of bias

Heikkinen 2000 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	double blind for the first 2 years and then single blind (participants only) thereafter however 2 groups had dose escalation after 6 months which may have compromised blinding in these groups
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for withdrawal well described
Free of other bias?	Unclear	6 parallel treatment groups, with some differences at baseline in % smokers and % previously used HT

HOPE 2001

Methods	Randomisation computer generated table, in blocks of 8 Multi-centre, double blind, placebo controlled. Number of women randomised: Basic study n = 2673. 2 year substudy n=822 Number of women analysed: Basic study n = 2153. 2 year substudy n=518 (analysed for the hyperplasia outcome) Number of withdrawals: n = 520. (lost to follow up) Source of funding: Wyeth-Ayerst Research, Philadelphia, Pensylvania
Participants	Country: USA Postmenopausal women with intact uterus, absence of menses for at least the past year, 17β estradiol levels< 184 pmol/l(50 pg/ml) and FSH levels > 30 IU/L, within 20% of their normal body weight range. Age: 40-65 years old Exclusion criteria: if taken medication containing estrogens, progestins, or androgens within 8 weeks of the pre study screening, endometrial hyperplasia diagnosed at baseline, specified intercurrent disease, smoking >15 cigarettes /day Substudy: intact uterus, 1-4 years post menopausal, baseline 17β estradiol</= 184 pmol/L and FSH levels >/= 30 IU/L and body weight within 20% of desirable weight range
Interventions	Unopposed E vs Continuousvs placebo (1) Conjugated equine estrogen(CEE) 0.625 mg daily. (2) CEE 0.625 mg/medroxyprogesterone(MPA) 2.5 mg/daily (3) CEE 0.45 mg (4) CEE 0.45 mg/MPA 2.5 mg/daily (5) CEE 0.45 mg/MPA 1.5 mg/daily (6) CEE 0.3 mg/daily (7) CEE 0.3 mg/MPA 1.5 mg/daily (8) Placebo/daily Duration: 1 year (13 cycles)

HOPE 2001 (*Continued*)

Outcomes	Endometrial hyperplasia,
Notes	The basic study was focused on menopausal symptoms, endometrial histology, and bleeding profiles. A two year substudy examined bone density and turnover, serum lipoproteins, and carbohydrate metabolism

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	planned outcomes reported but numbers and reasons of early withdrawals in each group not clearly described
Free of other bias?	Unclear	8 parallel groups; baseline characteristics described for the 69% of those randomised who completed the 2 year study

Koninckx 2005

Methods	Randomisation by global randomisation scheme following an allocation within each country by investigators. Multi centre,double blind Analysis: primary efficacy variable (hot flushes) by efficacy evaluable population, remainder by ITT Number randomised: 1218 (531 remained in study for year 2) Number premature withdrawals: 352 (main reason = adverse events)
Participants	Country: 98 sites in 8 countries (Belgium, Czech Republic, France, Germany, Israel, Switzerland, The Netherlands and UK Inclusion criteria: Postmenopausal women with an intact uterus, be amenorrhoeic for at least 6 months or have had HRTHT for at least 12 months, serum FSH greater than lower limit of normal for postmenopausal women, serum estradiol level lower than upper limit of normal for postmenopausal women, and at least hot flushes per day over a 7 day period. Exclusion criteria: known/suspected estrogen-dependant neoplasia, endometrial hyperplasia, polyp or carcinoma at screening,serious specified intercurrent disease
Interventions	sequential (A) 1mg 17β estradiol daily + 0.125mg trimegestone daily on days 15-28 (B) 1mg 17β E2 daily + 0.25mg trimegestone daily on days 15 -28

Koninckx 2005 (*Continued*)

	(C) 1mg estradiol valerate daily + 1 mg norethisterone daily on days 17-28 Duration:13 cycles	
Outcomes	bleeding profile, endometrial histology, safety	
Notes		

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Unclear	Endometrial biopsies on 801 women of 1218 randomised (66%) at end of treatment
Free of selective reporting?	Unclear	planned outcomes reported but reasons for withdrawal by 29% of those randomised not clearly described
Free of other bias?	Unclear	3 parallel groups. baseline characteristics given for efficacy evaluable population not all those randomised

Kurman 2000

Methods	Randomisation by computer using blocks of 8 Double-masked, randomised, parallel, controlled study in 40 centres. No of women randomised: n = 1176. Number of withdrawals: n = 251 Source of funding: Novo Nordisk Pharmaceutical.
Participants	Country: USA Inclusion criteria: Healthy women 45 years or older with an intact uterus, minimum 12 months post menopause, and serum E2 levels up to 25 pg/ml. Exclusion criteria: Women who had been treated with estrogen in the previous 12 weeks or with estrogen-progestogen combinations within the last 8 weeks; had known, suspected, or history of hormone dependent tumours or cancers; had known or suspected endometrial hyperplasia at study entry biopsy; had vaginal bleeding of unknown cause; were more than 30% above ideal body weight; had known deep vein thrombosis, active thrombophlebitis, thromboembolic disorder, cerebrovascular accident, or history of these conditions, had myocardial infarction or Ischaemic heart disease in the previous 6 months, had treated or untreated systolic blood pressure greater than 160 mmHg or diastolic BP greater than 100 mmHg, had presence of any endocrine disorder except

Kurman 2000 (*Continued*)

	controlled tyroid disease; were known alcohol or drug abusers; or had a known smoking habit of one pack of cigarettes a day or more
Interventions	Unopposed Evs continuous (1) 1 mg 17β-estradiol daily (2) 1mg 17β-estradiol + 0.1 mg norethindrone acetate daily (3) 1 mg 17β-estradiol + 0.25 mg norethindrone acetate daily (4) 1 mg 17β-estradiol + 0.5 mg norethindrone acetate daily Duration: 1 year
Outcomes	Frequency of endometrial hyperplasia/carcinoma Non-adherence to therapy
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	Yes	endometrial biopsies on 988 of the 1176 women randomised (84%)
Free of selective reporting?	Unclear	planned outcomes reported, but numbers and reasons for early withdrawal by group not clearly described
Free of other bias?	Yes	4 parallel groups well balanced at baseline

Luciano 1993

Methods	Randomisation method not stated. Single centre, parallel group design with double blinding. No of women randomised: n = 36. Number of withdrawals: n = 7. (in gp, 1due to recurrence of depression &1 due to exacerbation of migraine, in gp2, 1 due to exacerbation of hypertension, & in gp3 1 due to exacerbation of migraine and 3 due to cyclic bleeding) Source of funding: Upjohn (in part)
Participants	Postmenopausal women were recruited from newspaper advertisements and letters to GPs in Farmington, Connecticut. Inclusion criteria: intact uterus, no contraindication to HT, last menses at least one year prior, no HT for at least 6 months prior, oestradiol < 35 pg/mL and FSH < 50 mIU/mL.

Luciano 1993 (*Continued*)

	No exclusion criteria stated.
Interventions	continuous vs sequential (1) 0.625 mg CEE + 2.5 mg MPA daily (2) 0.625 mg CEE + 5.0 mg MPA daily (3) 0.625 mg CEE days 1-25 + 5.0 mg MPA days 14-25 Duration: 1 year
Outcomes	Frequency of irregular bleeding
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Endometrial biopsies on 30 of the 36 women randomised (83%)
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawal described
Free of other bias?	Unclear	small study with 3 parallel groups, some imbalance at baseline

Mattsson 2004

Methods	Randomisation: stratified and blocked by centre, all participants received treatment according to that allocated next consecutive study number Open randomised multicentre trial in 16 centres in Scandinavia Number of women randomised: 394 Number of women analysed: 393 Number of withdrawals: 1 woman who received no treatment Sources of funding: Orion Pharma, Finland
Participants	Countries: Norway, Denmark, Sweden Inclusion criteria:Postmenopausal women with intact uterus, aged 53-65 years, BMI less than or equal to 30, with at least one month since last dose of HT Exclusion criteria:Endometrial hyperplasia, contraindications to hormone therapy, previous use of comparator (2mg E2 +1mg NETA 'Kliogest')
Interventions	continuous (1)1-2 mg estradiol valerate (E2V) + 2.5 medroxyprogesterone acetate (MPA) daily (2)1-2 mg estradiol valerate (E2V) + 5 medroxyprogesterone acetate (MPA) daily

Mattsson 2004 (*Continued*)

	(3)2 mg estradiol valerate (E2V) + 1 mg norethisterone acetate (NETA) daily Duration:24 cycles
Outcomes	Mean number days of bleeding, amenorrhoea, endometrial biopsy, endometrial thickness
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	(A)
Blinding? All outcomes	No	open study
Incomplete outcome data addressed? All outcomes	Yes	255 of the 394 women randomised (65%) had endometrial biopsy at the end of treatment
Free of selective reporting?	Unclear	planned outcomes reported but numbers and reasons for early withdrawals in each group not clearly described
Free of other bias?	Yes	3 parallel groups well balanced at baseline

Meuwissen 2001

Methods	Randomisation method not stated, into 2 parallel groups Double blind, multi centre No randomised: 634 No premature withdrawals: 153 (74 in gp1 and 79 in gp 2, due to adverse events, (48 & 37 respectively, 7 from gp 1 due to lack of efficacy, and 47 (group not specified) due to protocol violation
Participants	Country: 56 centres in Europe, countries not specified. Inclusion criteria:Postmenopausal women with at least 6 mths amenorrhoea, or who had received HT for less than 12 mths after 6 mths amenorrhoea (washout period =2 mths) . At least 4 hot flushes per day and FSH and estradiol levels in postmenopausal range. Exclusion criteria: hysterectomy, serious specified intercurrent illness, endometrial hyperplasia/carcinoma at baseline biopsy
Interventions	sequential (A) 2mg 17 β estradiol daily + 0.5mg trimegestone daily on days 15-28 (B) Placebo days 1-7, 2mg 17β estradiol valerate daily days 8-28 + 0.5 norgestrel daily on days 19-28 Duration: 1 year (13 cycles)

Meuwissen 2001 (*Continued*)

Outcomes	endometrial histology, bleeding patterns
Notes	mean daily number hot flushes = primary efficacy variable. Numbers randomised to each group calculated from percentages reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	153 of the 634 women randomised (24%) withdrew during the study.End of treatment biopsies on 396 women (62%) of those randomised
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawal well described
Free of other bias?	Yes	2 parallel groups well balanced at baseline

MSG 1994

Methods	Methods of randomisation and allocation: computer generated schedule with packaged coded medication. Multicentre (99 sites), double-blind with parallel group design, placebo controlled. Number of women randomised: n = 1724. Number of withdrawals: n = 255 after 1 year of follow up; n = 339 after 2 years of follow up. Source of funding: Wyeth-Ayerst Research.
Participants	Countries: USA and Europe Healthy women aged 45-65 years with an intact uterus were recruited from 99 sites. Inclusion criteria: Last natural menstrual cycle at least 12 months before the baseline screening; FSH higher than the lower limit for postmenopausal women for the given laboratory; no use of estrogen- or progestogen-containing medication for at least 2 weeks before the pre study screening Exclusion criteria: Any contraindication for estrogen or progestogen use, or if they had used any estrogen containing medication within three months of entry; major medical illness, liver, kidney or diabetes; hypertension, systolic blood pressure greater than 160 mmHg or diastolic pressure greater than 90 mmHg; abnormal cervical cytology or endometrial hyperplasia at baseline biopsy

MSG 1994 (*Continued*)

Interventions	continuous vs sequential (1) 0.625 mg per day of conjugated equine estrogen (CEE), plus placebo (2) 0.625 mg per day of CEE plus 2.5 mg per day of medroxyprogesterone acetate (MPA) continuous (3) 0.625 mg per day of CEE plus 5 mg per day of medroxyprogesterone acetate (MPA) continuous (4) 0.625 mg per day of CEE plus 5 mg per day of (MPA) last 14 days of the cycle (days 15-28), plus placebo (days 1-14) (5) 0.625 mg per day of CEE plus 10 mg per day of (MPA) last 14 days of the cycle (days 15-28), plus placebo (days 1-14) Duration: one year (13 cycles)
Outcomes	Frequency of hyperplasia and/or carcinoma (confirmed by endometrial biopsy) at 6 and 12 months (at the end of cycles 6 and 13) Frequency of irregular bleeding or spotting (number of cycles)
Notes	If hyperplasia was confirmed, the patient was withdrawn from the study and given appropriate treatment

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Yes	Endometrial biopsies after one year of treatment on 1385 of the 1724 women randomised (80%)
Free of selective reporting?	Yes	planned outcomes reported in multiple publications
Free of other bias?	Yes	5 parallel groups well balanced at baseline

Nand 1995

Methods	Randomisation:method not stated, open study - no blinding Number of women randomised:32 Number of withdrawals: n = 9 (GpA 3, GpB 3, GpC 3)) Source of funding: Upjohn Pty.
Participants	Country:Australia Inclusion criteria: 1 year postmenopausal women with intact uterus and menopausal

Nand 1995 (*Continued*)

	symptoms. women already on HT had a 6 week washout period. Exclusion criteria: undiagnosed vaginal bleeding or specified serious intercurrent disease
Interventions	continuous (A) 1.5mg piperazine estrone sulphate + 2.5mg MPA daily (n=9) (B) 1.5mg piperazine estrone sulphate + 5mg MPA daily (n=11) (C) 1.5mg piperazine estrone sulphate + 10mg MPA daily (n=11) Duration:2 years
Outcomes	Bleeding pattern, endometrial biopsies, lipid levels, bone mineral density
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	No	open study
Incomplete outcome data addressed? All outcomes	Unclear	23 of the 32 women (72%) randomised had endometrial biopsies after 1 year
Free of selective reporting?	Yes	planned outcomes reported
Free of other bias?	Yes	3 parallel groups well balanced at baseline

Notelovitz 1997

Methods	A single randomisation schedule was generated by the Department of Biometrics, Solvay Pharmaceuticals, with 4-patient randomisation blocks of treatment distributed to each centre. Multicentre, parallel group and placebo controlled design with double-blinding. Number of women randomised: n = 280 (with intact uterus) of a total of 406. Number of withdrawals: n = 42 (before follow up endometrial biopsy). Number of patients analysed: n = 238 (54% of this group completed the study). Source of funding: Solvay Pharmaceuticals.
Participants	Country: USA. Healthy postmenopausal women with a uterus, aged 40-62, were recruited from 29 centres. Inclusion criteria: natural or surgical menopause (final menstrual period or oophorectomy between 6 months and 4 years prior to start of study; FSH>=50 IU/L; non smokers; 45-54 years of age (>21 years if documented bilateral oophorectomy; within 25% of ideal body weight (Metropolitan Height and Weight Tables). Exclusion criteria: bone mineral density >= 2 SD below normal peak for young adult

	women or evidence of vertebral compression fracture on screening radiography; treatment with estrogens or progestins within 8 weeks of enrolment; endometrial histology indicating either insufficient tissue in the presence of transvaginal ultrasound endometrial thickness of >4 mm or proliferative, hyperplastic or secretory endometrium; previous endometrial ablation; undiagnosed vaginal bleeding; estrogen dependent cancers; abnormalities of Pap smear or mammogram
Interventions	Unopposed E vs placebo (1) Esterified estrogen (ESE) 0.3 mg daily (2) ESE 0.625 mg daily (3) ESE 1.25 mg daily (4) Control: Placebo daily Duration 2 years
Outcomes	Frequency of endometrial hyperplasia at 6 and 12 months follow up Non-adherence to treatment Frequency of irregular bleeding Frequency of unscheduled endometrial biopsies (data not suitable for entry in the review)
Notes	We have reported the outcomes in this review for the women with an intact uterus n = 280 out of a total n = 406 in the study

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	218 of the 278 women randomised (78%) had endometrial biopsy after 2 years of treatment
Free of selective reporting?	Yes	planned outcomes reported and reasons and numbers of early withdrawals described
Free of other bias?	Yes	4 parallel groups well balanced at baseline

Obel 1993

Methods	Randomisation method and concealment of allocation not reported. Single centre, parallel group and placebo controlled design with double blinding. Number of women randomised: n = 151. Number of withdrawals: n = 22 (11 from treatment 1: 5 because of adverse events, 1 because of breast cancer, 5 for reasons unrelated to treatment; 5 from treatment 2: 3 because of adverse events, 2 because of carcinoma; 6 from placebo group: 1 because of adverse events, 1 because of anxiety, 1 for reasons unrelated to treatment). Source of funding: Not reported.
Participants	Country: Denmark Volunteers with early menopause (last spontaneous vaginal bleeding >6 and <24 months earlier) and with no use of HT during preceding 24 months recruited from Frederiksborg County. Exclusion criteria: previous or current estrogen-dependent neoplasia; thromboembolic disease, liver or pancreatic disease, diabetes mellitus, severe obesity, diseases with high or low bone turnover and medication known to influence bone metabolism or provoke induction of liver enzymes
Interventions	continuous vs sequential vs placebo (1) Continuous E2 2 mg + NETA 1 mg (Kliogest) daily (2) Sequential: Oestradiol (E2) 2 mg (days 1-12), E2 2 mg + norethisterone acetate (NETA) 1 mg (days 13-22), E2 1 mg (days 23-28) (3) Control: Placebo Duration: 2 years
Outcomes	Frequency of endometrial hyperplasia and/or carcinoma at 2 years Frequency of irregular bleeding Non-adherence to therapy
Notes	Some of the data was read off the graphs.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Blinding
Incomplete outcome data addressed? All outcomes	Yes	Endometrial biopsies on 96 of the 151 women randomised (64%) after 2 years
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawals described
Free of other bias?	Yes	3 parallel groups described as having 'no inter-group differences'

OGEN-Provera 1998

Methods	Method of Randomisation: Randomisation by computer code stratified by previous HT use, in blocks of 6 to facilitate even distribution of groups within each centre, Multicentre (9 sites), double blind with regard to progestogen dose, parallel groups. Number of women randomised: n = 568. Number of withdrawals: n = 146 (GpA 50, GpB49, GpC 47) Source of funding: Statistical support from Pharmacia and Upjohn
Participants	Country: Australia Inclusion criteria: healthy post menopausal women with intact uterus & 1-10 years of amenorrhoea, with climacteric symptoms requiring therapy. Previous users of HT had at least 6 week washout period. FSH > 40 IU/L. Exclusion criteria: Severe intercurrent disease.
Interventions	continuous (A) 1.5mg piperazine estrone sulphate + 2.5mg MPA daily (n=189) (B) 1.5mg piperazine estrone sulphate + 5mg MPA daily (n=185) (C) 1.5mg piperazine estrone sulphate + 10mg MPA daily (n=183) Duration:2 years
Outcomes	Primary Outcome: cessation of vaginal bleeding Secondary outcomes: protection of endometrium, maintenance of acceptable blood lipid profile, maintenance of bone mineral density and improvement of climacteric symptoms
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Endometrial biopsies after 2 years on 415 of 568 women randomised (73%)
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawals described
Free of other bias?	Yes	3 parallel groups well balanced at baseline

Okon 2001

Methods	Randomisation: computer generated codes, with allocation concealed in sealed envelopes. Single centre double blind parallel group design Number of women randomised: 33 Number of women analysed:23 Number of early withdrawals: 10 (main reasons were hormone related side effects e.g. fluid retention, weight gain, depression, breast tenderness) Funding: Schering
Participants	Countries: Denmark, Norway and Sweden. Inclusion criteria:women recruited aged 45-65 years (mean 52 +/- 4 years) who had amenorrhoea for 12 - 72 months, serum FSH >20 IU/L, plasma estradiol </= 30 pmol/l, intact uterus and requesting HT Exclusion criteria: Women with a pathological biopsy at study entry, or abnormal liver or renal function test results
Interventions	sequential (1) 2mg 17 beta estradiol daily + 25 µg gestodene added days 17-28 (2) 2mg 17β E2 daily + 50µg gestodene added days 17-28 Duration: 1 year
Outcomes	Endometrial hyperplasia, bleeding patterns,
Notes	PP14 and CA125 levels in endometrial flushing solutions.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	23 of the 33 women randomised (70%) who completed the study had endometrial biopsies after 1 year of treatment
Free of selective reporting?	Unclear	planned outcomes reported but 30 % of those randomised withdrew from the study, were excluded from analysis and numbers/reasons per group not described
Free of other bias?	Yes	small trial 2 parallel groups, no differences at baseline

PEPI 1995

Methods	Methods of randomisation and allocation: computer generated. Treatment group assignment was stratified by clinical centre and uterine status (hysterectomy status). Multicentre (7 clinical centres), parallel group, placebo controlled design with double blinding. Number of women randomised: n = 596 Number of women analysed: n = 596 (no exclusions post randomisation). Source of funding: Wyeth-Ayerst Laboratories.
Participants	Country: USA 875 healthy postmenopausal volunteers (596 with a uterus, 279 without a uterus), aged 45-65 years (average 56.2 years) were recruited via a national mass media campaign. Inclusion criteria: good health; willing to accept random assignment to a hormone therapy or placebo; cessation of menses for at least one year, but not more than 10 years prior to enrolment; surgically menopausal at least 2 months after hysterectomy; FSH levels >= 40 IU/L; normal atrophic endometrial biopsy and mammography results at baseline. Exclusion criteria: breast or endometrial cancer; any other cancer except non-melanomatous skin cancer diagnosed < 5 years before baseline; serious medical illness (myocardial infarction within six months, congestive heart failure, stroke, transient ischaemic attack); severe menopausal symptoms; use of HT within previous 2 months; hyper- or hypothyroidism; normal pelvic examination, Papanicolaou test and endometrial biopsy
Interventions	Participants randomised to equal numbers to one of the following oral treatments in 28 day cycles: Unopposed E vs continuous vs sequential vs placebo (1) 0.625 mg per day of conjugated equine estrogen (CEE) (2) 0.625 mg per day CEE + 10 mg per day of Medroxyprogesterone acetate (MPA) for the first 12 days per month (sequential) (3) 0.625 mg per day CEE + 2.5 mg per day of MPA (continuous) (4) 0.625 mg per day CEE + 200 mg per day of cyclic micronized progesterone for the first 12 days per month (sequential) (5) Control: Placebo Duration: 3 years
Outcomes	Frequency of hyperplasia or carcinoma (confirmed by endometrial biopsy) annually (at 12, 24 and 36 months) Frequency of unscheduled biopsies or dilatation and curettage Non-adherence to therapy Diary of symptoms, reports of vaginal bleeding, medication use and interim illnesses was reviewed. Visits at three, six and twelve months first year, six months thereafter for a total of three years
Notes	39 women were unblinded because of endometrial biopsy results classified as complex hyperplasia, atypia or carcinoma. 32 of these were from the unopposed estrogen group (group 1) , 3 were receiving placebo, and 4 were receiving one of the O + P regimens
Risk of bias	

PEPI 1995 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	yes
Free of selective reporting?	Yes	all planned outcomes reported in multiple publications
Free of other bias?	Yes	5 parallel groups well balanced at baseline.

Portman 2003

Methods	Randomisation:computer generated block randomisation in blocks of 8 Multi centre, blinding unclear - participants in 6 treatment groups "blinded to placebo" but control group was open label Number of women randomised: 945 Number of women analysed: 936 (ITT population) Number of withdrawals: 288 (116 due to adverse events - details not specified) Source of funding: Not stated
Participants	Country: USA Inclusion criteria: at least 40 years old, with intact uterus and less than 5 years post natural menopause, amenorrhoea for at least 6 months, FSH >/= 50 IU/L and estradiol </= 20 pg/ml, BMI <31, washout period required for those previously taking HT. Exclusion criteria: any contraindication to HT, significant intercurrent disease (specified) , use of bisphosphonate or calcitonin, use of other specified concomitant medications
Interventions	Unopposed E vs continuous (1) 5µg estradiol (E2) + 0.25mg norethisterone acetate (NETA) daily (2)5µg estradiol (E2) + 1mg norethisterone acetate (NETA) daily (3) 10µg estradiol (E2) + 0.5mg norethisterone acetate (NETA) daily (4)10µg estradiol (E2) + 1mg norethisterone acetate (NETA) daily (5) 5µg estradiol (E2) unopposed (6) 10µg estradiol (E2) unopposed (7) 0.625 mg conjugated equine estrogens (CEE) + 2.5mg medroxyprogesterone acetate (MPA) daily Duration:12 cycles
Outcomes	Endometrial hyperplasia, withdrawal due to adverse events
Notes	
Risk of bias	

Portman 2003 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	Unclear	Participants 'blinded to placebo' except for group 7 which was an 'open label control group'
Incomplete outcome data addressed? All outcomes	Unclear	all participants in the ITT population had biopsy results reported (those who withdrew had last observation carried forward)
Free of selective reporting?	Yes	planned outcomes reported and reasons and numbers for early withdrawals described
Free of other bias?	Yes	8 parallel groups, well balanced at baseline

Prestwood 2003

Methods	Randomisation:by computer generated list held by the research pharmacist and concealed from investigators Design: parallel group, placebo controlled, double blind, single centre Number of women randomised:167 (115 with intact uterus) Number of women analysed:167 Number of withdrawals: 55 (24 in GpA, 31 in placebo) Funding by grants from Claude Pepper Older Americans Independence Center, General Clinical Research Center and the Paul Beeson Physician Faculty Scholars in Aging Research program, and the calcium and vitamin D were provided by Mission Pharmacal
Participants	Country:United States of America Inclusion criteria: healthy community-dwelling women over 65 years Exclusion criteria: specified past of intercurrent diseases and medications affecting bone metabolism, estrogen or calcitonin in previous 6 months, ever use of bisphosphonate or fluoride
Interventions	long cycle sequential vs placebo (A) 0.25mg 17β E2 daily + 100 mg micronised progesterone daily for 2 weeks every 6 months (B) placebo All participants took 1300 mg/day of calcium and 1000 IU/day of Vitamin D Duration:3 years
Outcomes	Bone mineral density(hip) ,endometrial hyperplasia, bleeding patterns
Notes	

Risk of bias

Prestwood 2003 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	No	112 of the 167 women randomised completed the study. Not clear how many of those with intact uterus completed the final endometrial biopsy
Free of selective reporting?	Yes	planned outcomes reported but numbers and reasons for early withdrawals
Free of other bias?	Yes	2 parallel groups well balanced at baseline

Rees 2004

Methods	Study 1 Randomisation: method not stated Multicentre, parallel group, double blind Number of women randomised: n = 399 Number of withdrawals: n = 6 (failed to take any medication) Source of funding: Orion Pharma, Espoo, Finland Study 2 Randomisation: method not stated Multicentre, parallel group, no blinding Number of women randomised: n = 341 Number of withdrawals: n = 1 (failed to take any medication) Source of funding: Orion Pharma, Espoo, Finland
Participants	Postmenopausal women with intact uterus, at least 6 months since last menstruation or serum FSH > 30 IU/ml, BMI not exceeding 32 +/- 1, washout period of at least 1 month for those previously on HT Age: 40-65 years old from 31 centres in UK (10), France(6) & Germany(15) Exclusion criteria: endometrial hyperplasia, endometriosis, endometrial fibroids >1 cm, undiagnosed uterine bleeding, abnormal mammography & gynaecological status, thromboembolic disorders, uncontrolled hypertension. Country: Germany & France (Study 1); UK (Study 2)
Interventions	Study 1 Triphasic: 2mg Estradiol valerate daily (9 days), then 2mg E2V + 10 mg MPA daily (12 days), then 1mg E2V daily (7 days) Biphasic: 2mg E2V daily (11 days), then 2mg E2V + 10mg MPA daily (10 days) then placebo (7 days) Duration:12 or 13 cycles Study 2

	Triphasic:2mg Estradiol valerate daily (9 days), then 2mg E2V + 10 mg MPA daily (12 days), then 1mg E2V daily (7 days) Triphasic:2mg estradiol + 1mg estriol daily (12 days) then 2mg estradiol +1mg estriol+1mg norethisterone acetate daily (10 days) then 1mg estradiol + 0.5mg estriol daily (6 days) Duration: 12 or 13 cycles
Outcomes	Endometrial biopsy (primary) endometrial thickness, cycle control, climacteric symptoms
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Yes	only Study one is blinded
Incomplete outcome data addressed? All outcomes	Unclear	In study one, 202 of 399 women randomised completed the study (51%) but it is not clear how many of these women had endometrial biopsy at treatment end In study two, 167 of 341 women randomised, completed the study (49%) but it is not clear how many of these women had endometrial biopsy at treatment end
Free of selective reporting?	Unclear	planned outcomes all reported and reasons for early withdrawal described
Free of other bias?	Unclear	3 parallel groups well balanced at baseline, but only study one was blinded so bias is possible

Rozenberg 2001

Methods	Randomisation method not stated. Multi-centre, for the first year subjects and investigators were blinded to sequential therapy groups, continuous group not blinded, parallel design. An extension study continued open label treatment of 1mg E2 + sequential intermittent 90 µg norgestimate compared to continuous 2 mg E2 + 1 mg NETA Number of women randomised: n = 657 Number of withdrawals: n = 186 (45 in group 1, 109 in group 2, 32 in group 3) Source of funding: not stated.
Participants	Postmenopausal women with serum E2 concentration<20 pg/ml, FSH > 40 IU/ml, BMI within 30 % of the average BMI for age and no contraindications to estrogen and or progestogen therapy. Age: 40-65 years old from 42 centres in Belgium, Finland, Sweden, Netherlands. Exclusion criteria: history of using other hormonal therapies prior to screening within 6 weeks, injectable or implantable steroids 6 months before screening
Interventions	intermittent sequential vs continuous (1) 1 mg 17β-estradiol (E2) daily + 90 µg norgestimate (NGM) days 4-6, 10-12, 16-18 etc (seq) (2) 2 mg 17β-estradiol (E2) daily + 180 µg norgestimate (NGM) days 4-6, 10-12, 16-18 etc (seq) (3) 2 mg 17β-estradiol + 1 mg NETA (norethisterone acetate) daily (cont)
Outcomes	Endometrial hyperplasia Withdrawal
Notes	Same study as Ylikorkala 2002 but different outcomes

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Incomplete outcome data addressed? All outcomes	Yes	After 2 years 282 of the 322 women randomised (88%) had an endometrial biopsy
Free of selective reporting?	Yes	planned outcomes reported and early withdrawals well described
Free of other bias?	Yes	3 parallel groups well balanced at baseline

Scandinavia 1996

Methods	Randomisation method not stated. Multi-centre, parallel group design, blinding not clear. Number of women randomised: n = 240. Number of exclusions: not given. Source of funding: not given.
Participants	Countries: Denmark, Norway and Sweden. 240 women recruited aged 45-65 years (mean 52 +/- 4 years) who had been post-menopausal for at least 1 year. No other inclusion or exclusion criteria given.
Interventions	Long cycle Sequential vs monthly sequential (1) HT with extended cycle of 84 days: 2 mg of 17β estradiol for 68 days; 2 mg of 17β-estradiol and 1 mg of norethindrone acetate for 10 days and 1 mg of 17β-estradiol for 6 days. (2) HT with a regular cycle of 28 days (monthly cycle HT): 2 mg of 17β estradiol for 12 days; 2 mg of 17β-estradiol and 1 mg of norethindrone acetate for 10 days, and 1 mg of 17β-estradiol for 6 days. Duration: planned to be 5 years but terminated early after 4 years. (mean duration of long cycle group 2.8 years)
Outcomes	Endometrial hyperplasia or carcinoma
Notes	Authors contacted regarding randomisation method, blinding, number of withdrawals, whether a power calculation and intention to treat analysis was performed. Trial discontinued before 5 years due to safety analysis. The study was discontinued because of the unsatisfactory safety profile of the long-cycle hormone regimen

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Incomplete outcome data addressed? All outcomes	Unclear	After one year of treatment 195 of 240 women randomised (81%) had an endometrial biopsy. Trial was stopped early and numbers of women biopsied after 2 and 3 years of treatment are unclear
Free of selective reporting?	Yes	planned outcomes were endometrial histology and reasons and numbers of early withdrawal from the trial well documented
Free of other bias?	Yes	2 parallel groups balanced at baseline for age, BMI and previous HT use

Sporrong 1988

Methods	Randomisation: randomisation tables Single centre, double blind parallel group study Number of women randomised: 60 Number of withdrawals:12. (7 due to gastrointestinal disturbances, 4 due to depression/ irritability and 1 due to deep vein thrombosis) Source of funding: not stated.
Participants	Country: Sweden Inclusion criteria: Postmenopausal women attending outpatient clinic for climacteric complaints, who were otherwise healthy, had intact uterus, no contraindications to HRTHT and had ceased menstruation at least 1 year prior to study. no hormone treatment was given for 6 weeks prior to the start of the study
Interventions	continuous (A) 2 mg 17β estradiol + 1 mg norethisterone acetate (NETA) daily (B) 2 mg 17β estradiol + 0.5 mg norethisterone acetate (NETA) daily (C) 2 mg 17β estradiol + 5 mg megestrol acetate (MEGA) daily (D) 2 mg 17β estradiol + 2.5 mg megestrol acetate (MEGA) daily Duration: 1 year
Outcomes	Endometrial hyperplasia Mean number days with bleeding Amenorrhoea at 4 months
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	double blind
Incomplete outcome data addressed? All outcomes	Unclear	48 of the 60 women randomised (80%) had endometrial biopsy after 1 year
Free of selective reporting?	Yes	planned outcomes reported
Free of other bias?	Yes	4 parallel groups well balanced at baseline

Stadberg 1996

Methods	Single centre double blind trial, randomised in blocks of 9 to 3 parallel treatment groups Number randomised: 60 Number analysed:49 Number withdrawals: 11 (5, 2, 4 from groups 1,2, and 3 respectively) due to insufficient effect on vasomotor symptoms (n=2 Gp 1,n= 2 Gp 3), spotting (n=2 Gp 1) leg cramps (n=1 Gp1), urinary tract infections (n=2 Gp2) depression (n=1 Gp 3), bleeding disorders (n=1 Gp3) Source of funding: grants from Hjalmar Svensson's fund and Goteborg Medical Society at University of Goteburg. NOVO industries A/S supplied the tablets
Participants	Country: Sweden Inclusion criteria: postmenopausal women with climacteric complaints, either had a natural menopause or used HT for >3 years, an intact uterus, and 6 week washout for previous users of HT Exclusion criteria: serious intercurrent illness, contraindications for hormone therapy
Interventions	continuous (1) 1 mg 17β estradiol (E2) + 0.25 mg norethisterone acetate (NETA) daily (2) 1 mg 17β estradiol (E2) + 0.5 mg norethisterone acetate (NETA) daily (3) 1 mg 17β estradiol (E2) + 1 mg norethisterone acetate (NETA) daily Duration: 1 year
Outcomes	Bleeding patterns at 12 months, Endometrial hyperplasia
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	Endometrial biopsies after 1 year were obtained in 49 of the 60 women randomised (82%)
Free of selective reporting?	Yes	planned outcomes reported and reasons for early withdrawal well documented
Free of other bias?	Unclear	3 parallel groups with differences at baseline in mean age and weight of participants

van de Weijer 1999

Methods	Randomisation method not stated, medication separately packaged for each participant and labelled with code number. Double blind parallel group study in 2 centres in the Netherlands Number women randomised: 151 1 post randomisation exclusion due to endometrial carcinoma at baseline. No women analysed:129 (64 in low dose group, 67 in high dose group) Number women prematurely withdrawn: 17 due to bleeding problems (n=3, 2 in low dose, 1 in high dose), minor AE's (n=11) lack of efficacy (n=1) gynae problems unrelated to study (n=1) lost to follow up (n=1), non compliance (n=2)
Participants	Country: The Netherlands Inclusion criteria: healthy, non-hysterectomised women aged 45-65 years, with at least 6 months amenorrhoea, serum FSH >35 IU/L and a baseline endometrial biopsy showing non-secretory, non-hyperplastic, non-malignant endometrium Exclusion criteria: any contraindication to estrogen use, concomitant medications known to influence study measurements, HT within 4 weeks of first screening visit
Interventions	sequential (A) 1mg micronized 17β estradiol daily + 5mg dydrogesterone daily on days 15-28 of each cycle (B) 1mg micronized 17β estradiol daily + 10mg dydrogesterone daily on days 15-28 of each cycle Duration: 13 cycles
Outcomes	Bleeding pattern, endometrial biopsy,
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	124 of the151 women randomised had endometrial biopsies after 1 year
Free of selective reporting?	Unclear	planned outcomes reported but numbers and reasons for early withdrawal in each group not clear
Free of other bias?	Yes	2 parallel groups balanced at baseline

Warming 2004

Methods	Method of randomisation: block randomised using random numbers Double-blind placebo controlled single centre study Number of women randomised: 240 Number of women analysed: ?180/?240 Number of withdrawals: 60 (lack of efficacy (2), HT related AE's (35), other AE's (11), breast cancer (1) Pulmonary embolus (1) other (10) Sources of funding: Schering AG, Berlin
Participants	Country: Denmark Inclusion criteria: 45-60 year women at least one year post natural menopause Exclusion criteria: Systemic disease, diseases of bone metabolism, abnormal blood & urine lab tests, history of malignancy
Interventions	continuous vs placebo (1) 1 mg 17β estradiol + 1 mg drospirinone daily (2) 1 mg 17β estradiol + 2 mg drospirinone daily (3) 1 mg 17β estradiol + 3 mg drospirinone daily (4) placebo Duration: 24 months
Outcomes	Endometrial hyperplasia, Withdrawals due to AE's, Amenorrhoea, bleeding patterns
Notes	BMD, biochemical markers of bone metabolism, lipid profiles

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	
Incomplete outcome data addressed? All outcomes	Unclear	180 of the 240 women (75%) randomised had endometrial biopsies after 2 years
Free of selective reporting?	Yes	planned outcomes reported and numbers and reasons for early withdrawals in each group described
Free of other bias?	Yes	4 parallel groups balanced at baseline

WHI 2002

Methods	Randomisation: Centrally randomised by permuted block algorithm, stratified Stratification: By clinical centre site and age group Allocation: By local access to study database Blinding: All participants, clinic staff, and outcome assessors blinded, with the exception of 331 participants who were unblinded and reassigned to experimental group due to change in protocol (see notes) Unblinding: When required for safety or symptom management, un blinding officer unblinded clinic gynaecologist, who was not involved with outcomes assessment. At average 5.2 year follow-up, 3444 women in experimental group and 5448 women in placebo group had been unblinded, mainly to manage persistent vaginal bleeding) No randomised: 16,608 (8506 to experimental group, 8102 to placebo group) Losses to follow-up: 583 participants (3.5%) - i.e. no outcomes data for > 18 months: [307 in HT arm (3%), 276 in control arm (3.5%). Vital status known for 96.5% Non adherence to allocated treatment: by 5.2 years (median): 42% experimental arm, 10.7% placebo arm. 432 women, 248 in experimental arm, 183 in placebo arm, who had hysterectomy after randomisation (for reasons other than cancer) switched to unopposed estrogen or corresponding placebo Withdrawals: 583 lost to follow-up (3.5%) or stopped providing outcomes information for more than 18 months
Participants	Inclusion criteria: Postmenopausal women (no vaginal bleeding for 6 months, or for 12 months for 50-54 year olds; any use of postmenopausal hormones), with a uterus, aged 50-79 at initial screening, likely to reside in area for 3 years, provision of written informed consent Exclusion criteria: Medical condition predictive of survival time <3 years, invasive cancer in past 10 years (except non-melanoma skin cancer), breast cancer at any time or suspicion of breast cancer at baseline screening, acute myocardial infarction, stroke, transient ischaemic attack in previous 6 months, known chronic active hepatitis or severe cirrhosis, blood counts indicative of disease, severe hypertension or current use of oral corticosteroids, femoral neck bone mineral density of more than 3 standard deviations below the corresponding age-specific mean, endometrial cancer or endometrial hyperplasia at baseline, malignant melanoma, pulmonary embolism or deep vein thrombosis that was nontraumatic or that had occurred in the previous six months, bleeding disorder, lipaemic serum and hypertriglyceridaemia diagnosis, current use of anticoagulants or tamoxifen, PAP smear or pelvic abnormalities, unwillingness or inability to complete baseline study requirements, alcoholism, drug dependency, mental illness, dementia, severe menopausal symptoms inconsistent with assignment to placebo, inability or unwillingness to discontinue current HT use or oral testosterone use, inadequate adherence with placebo run-in, unwillingness to have baseline or follow up endometrial aspirations, active participant in another randomised clinical trial Mean age: 63 years (SD 7) Age range: 50-79. Age ratio of 33%:45%:21% for the baseline age categories of 50-59, 60-69, 70-79 respectively (enrolment targeted to achieve ratio of 30:45:25) Recruitment: Letter of invitation in conjunction with media awareness programme. Sampling method gave women from minority groups six-fold higher odds for selection than Caucasian women and resulted in sample with 84% racially/ethnically designated "white", 16% non-"white" Screening: Interested women screened by phone or mail for eligibility, then attended 3 screening visits for history, clinical exam and tests. Three month washout period before

	baseline evaluation of women using postmenopausal hormones at baseline screening. Lead-in placebo pills given for at least 4 weeks during screening process to establish compliance with pill taking. Baseline equality of treatment groups: No substantive differences between study groups at baseline Country: USA
Interventions	continuous vs placebo (1) Combined estrogen and progesterone as one daily tablet containing conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg (0.625 mg CEE plus 2.5 mg MPA daily) (2) Control group: Matching placebo Duration:planned 8 years stopped after 5.2 Permanent discontinuation of medication: Women who developed breast cancer, endometrial hyperplasia not responsive to treatment, endometrial atypia, endometrial cancer, deep vein thrombosis, pulmonary embolus, malignant melanoma, meningioma, triglyceride level over 1000 mg/dL, prescription of estrogen, testosterone or selective estrogen-receptor modulators by their personal physician. Temporary discontinuation of medication: women who had acute MI, stroke, fracture, major injury involving hospitalisation, surgery involving anaesthesia, illness resulting in immobilisation for over one week, or other severe illness in which hormone use temporarily inappropriate
Outcomes	Cardiovascular disease: acute MI, silent MI, coronary death, stroke, pulmonary embolus Cancer: breast, colorectal, endometrial, other cancers Fractures: Hip, vertebral, osteoporotic
Notes	Power: 88% power to detect intervention effect of 21% for CHD over 9 years; 73% power to detect 21% difference in hip fractures over 9 years ; 99% power to detect 20% difference in all fractures over 9 years; 79% power to detect 22% difference in breast cancer incidence over 9 years. (All at 2 sided p = 0.05) Planned 8.5 years follow up. Trial stopped after 5.2 years as test statistic for breast cancer exceeded stopping boundary. After release of PEPI trial results indicating long term adherence to unopposed estrogen was not feasible in women with a uterus, the WHI protocol was changed to randomise women with a uterus to only estrogen plus progestin or placebo in equal proportions. The 331 women previously randomised to unopposed estrogen were unblinded and reassigned to estrogen plus progestin

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	(A)
Blinding? All outcomes	Yes	

WHI 2002 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	follow up data for 96.5% of those randomised.
Free of selective reporting?	Yes	planned outcomes reported in multiple publications and numbers and reasons for early withdrawal described
Free of other bias?	Yes	2 parallel groups well balanced at baseline

Williams 1994

Methods	Randomisation; method not stated Placebo controlled double blind study undertaken at 2 centres in the USA Number of women randomised:80 Number of women analysed: 62 Number of women withdrawn:18 - 8 following non-serious medical events, 4 for personal reasons, 2 lost to follow up, one ineligible due to abnormal mammogram, 3 for 'other' reasons Funding:grant from Upjohn company
Participants	Country: USA Inclusion criteria: postmenopausal women with intact uterus with amenorrhoea for at least one year, normal endometrial histology, FSH greater than 50mIU/l and serum estradiol less than 30 pg/ml. Women had not had injectable hormone therapy in the year prior to the start of the study or oral therapy in the month prior. All were within 30% of ideal body weight. Exclusion: History of cancer, alcohol or drug abuse, current pv bleeding or serious intercurrent illness (specified)
Interventions	sequential monthly vs long cycle (1) 0.625 mg CEE daily + 10 mg MPA on days 15-28 (14/28 group) (2) 0.625 mg CEE daily + 10 mg MPA on days 71-84 (14/84 group) (3) 0.625 mg CEE daily + 10 Mg MPA on days 57-84 (28/84 group) In all groups a placebo tablet was given daily on the progestogen free days
Outcomes	Bleeding patterns, endometrial histology
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Double blind

Williams 1994 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	62 women of the 80 randomised (78%) had endometrial biopsy after 12 cycles of treatment
Free of selective reporting?	Unclear	planned outcomes reported, numbers and reasons for early withdrawals in each group not clearly described
Free of other bias?	Yes	3 parallel groups balanced at baseline

Wu 2002

Methods	Randomisation;method not stated No blinding of participants or researchers, study undertaken at 3 medical centres Number of women randomised: 236 Number of women analysed: 213 at 1 year , 176 at 2 years Number of withdrawals: n = 60 Source of funding: Wyeth-White Hall Pharmaceuticals provided the CEE and Vitamin D tablets
Participants	Country: China Women 1-4 years postmenopause, with an intact uterus, endometrial thickness less than 5 mm, BMI 18-28. Exclusion criteria: Thrombotic diseases, coronary heart disease, scoliosis, L2-4 BMD less than -2.5 SD, exogenic hormone use in previous 3 months, calcitonin or biphosphate in previous 6 months or fluoride in previous 12 months
Interventions	continuous vs no treatment (A) 0.625 mg CEE + 2 mg MPA + Caltrate D (Vitamin D) daily (B) 0.3mg CEE + 2 mg MPA + Caltrate D daily (C) Caltrate D only
Outcomes	Endometrial thickness and biopsy
Notes	Other outcomes BMD, breast tenderness, bone metabolic markers, vaginal bleeding

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	No	Not mentioned
Incomplete outcome data addressed? All outcomes	Unclear	103 of the 236 women randomised (44%) had endometrial assessment after 2 years

Free of selective reporting?	Unclear	planned outcomes reported but numbers and reasons for early withdrawal not clearly described
Free of other bias?	Yes	3 parallel groups balanced at baseline

Yildirim 2006

Methods	Randomisation: method not stated single blind, single centre randomised trial Number of women randomised: 246 Number of women analysed: 204 Number of withdrawals: Gp 1 27 (11 due to adverse events including vaginal bleeding, mastodynia and headache) Gp2 15 (9 due to adverse events including vaginal bleeding, mastodynia and headache) Sources of funding: not mentioned
Participants	Country: Turkey Inclusion criteria:healthy postmenopausal women aged 41 to 57 years, with vasomotor, psychological or atrophic symptoms, intact uterus and ovaries, normal endometrial thickness, at least 12 months of amenorrhoea, and vasomotor symptoms. women had to have normal blood biochemical levels, normal cervical smear and bilateral mammography Exclusion criteria:
Interventions	continuous (1) 0.625 mg conjugated equine estrogens (CEE) +2.5 mg medroxyprogesterone acetate (MPA) daily (2) 1 mg estradiol (E2) + 0.5 mg norethisterone acetate (NETA) daily Duration:12 months
Outcomes	bleeding/spotting at 3,6,9,12 months, amenorrhoea at 12 months
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Unclear (B)
Blinding? All outcomes	Yes	Single blind
Incomplete outcome data addressed? All outcomes	Unclear	72 women of the 246 randomised (29%) had endometrial biopsy after 1 year
Free of selective reporting?	Unclear	planned outcomes reported but

Yildirim 2006 (*Continued*)

Free of other bias?	Unclear	2 parallel groups with unequal numbers and differences at baseline in duration of menopause and parity

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aoki 1990	This trial has published in abstract form and located by handsearching. No indication was given whether women were randomised to treatment groups and attempts were made to contact the author for clarification but no reply was received
Archer 1999	Outcomes are adherence to treatment and bleeding patterns. No data on endometrial hyperplasia
Archer 2001	Excluded as amenorrhoea is primary outcome. No hyperplasia outcome data
Arrenbrecht 2004	Primary outcomes related to bone density and bleeding. No data on endometrial hyperplasia
Blumel 1994	Primary outcome is bleeding patterns after 6 months therapy. No hyperplasia outcome data
Byrjalsen 1992a	Bleeding outcomes only. No hyperplasia outcome data.
Byrjalsen 1992b	No hyperplasia outcome data reported
Campbell 1977	This trial is excluded because endometrial hyperplasia at baseline is not an exclusion criterion for entry into the trial (exclusion criterion for this review is any contraindication to HT)
Campodonico 1996	Primary outcome is amenorrhoea.
Chen 1999	Primary outcomes are bleeding patterns. No hyperplasia data reported
Christensen 1982	Primary outcomes are bleeding patterns. No hyperplasia data reported
Granberg 2002	Trial not randomised
Gulhan 2004	Article in Turkish language with English language abstract. The outcome is endometrial thickness by ultrasound
Hagen 1982	Primary outcomes are bleeding patterns. No hyperplasia data reported
Heytmanek 1990	This trial was published in abstract form and was located by handsearching. No indication was given whether women were randomised to treatment groups and attempts were made to contact the author for clarification but no reply was received

(*Continued*)

Istre 1996	Excluded because all participants underwent transcervical resection of endometrium prior to starting the study
Jaisamrarn 2002	Excluded because bleeding outcomes only
Jirapinyo 2003	Primary outcomes are bleeding patterns. No hyperplasia data reported
Kazerooni 2004	Primary outcome is cumulative amenorrhoea rates.
Keil 2002	Study only 4 months in length. Protocol states studies should be at least 1 year in length
Limpaphayom 2000	Primary outcomes are bleeding patterns and climacteric symptoms. No endometrial hyperplasia data
Liu 2005	Primary outcomes are bone indices. No endometrial hyperplasia data
Luciano 1988	Study only 4 months in length. Protocol states studies should be at least 1 year in length
Marslew 1991	Primary outcomes are bleeding patterns and adherence to therapy
Marslew 1992	Primary outcomes are bleeding patterns and adherence to therapy
Mizunuma 1997	Primary outcomes are bleeding patterns
Morabito 2004	This study (together with conference abstract by Crisafulli) had BMD as primary outcome. Endometrial biopsy was not planned a priori, and were undertaken on only 8 women who had endometrial thickness greater than 5 mm
Nachtigall 1979	Trial was based on 84 matched pairs that were randomised to treatment or placebo. However, participants were hospitalised with long term chronic disease which is an exclusion criterion for this review
Odmark 2001	Trial compared the bleeding patterns of women who had started hormone therapy for the first time with the bleeding patterns of those who 'switched' (without a washout period) from an alternative hormone therapy regimen. Washout period for previous hormone users is an inclusion criteria, No endometrial hyperplasia data
Pinto 2003	Nine months therapy only given to frail elderly women.
Popp 2006	5 of the 73 women randomised (7%) had endometrial hyperplasia at baseline. Protocol states that participants must have either normal endometrial histology by biopsy or endometrial thickness less than 5 mm
Schiff 1982	Comparison is estrogen (cyclic) vs estrogen continuous, an obsolete regimen which does not meet the inclusion criteria for studies included in this review
Simon 2001	Primary outcomes are bleeding patterns. No data on endometrial hyperplasia
Simon 2003	Primary outcomes are adverse events and withdrawals. No data on endometrial hyperplasia

(*Continued*)

Steiner 2007	EPAT (estrogen in the prevention of atherosclerosis trial) was conducted from April 94 to Nov 98. Women recruited from newspaper ads targeting employees of universities and HMO's. 220 women randomised to estrogen only or placebo. WELLHART (Women's Estrogen -Progestin Lipid Lowering Hormone Atheroscelerosis Regression Trial) is a randomised trial of 448 women recruited from angiography clinics and randomised to usual care, estrogen only or estrogen + progestin. Steiner et al combined the outcome data from the estrogen only groups of these trials and compared them to those from the WELLHART trial who took estrogen and progestogen, with regard to the outcome of endometrial hyperplasia. This is retrospective analysis of participants from different populations, randomised at different times according to different criteria. Excluded
Stevenson 2001	Primary outcomes are bone mineral density and amenorrhoea. No data on endometrial hyperplasia
Sturdee 1996	This trial was published in abstract form and was located by handsearching. No indication was given whether women were randomised to treatment groups and attempts were made to contact the author for clarification but no reply was received
Sturdee 2000	No indication was given whether women were randomised to treatment groups and attempts were made to contact the author for clarification but no reply was received
Symons 2000	Study only 4 months in length. Protocol states studies should be at least 6 months in length
Symons 2002	Study duration only 6 months and outcomes bleeding patterns.
Ulla Timonen 2002	This trial was published in abstract form and was located by handsearching. No indication was given whether women were randomised to treatment groups and attempts were made to contact the author for clarification but no reply was received
Utian 2002	Study only 3 months in length. Protocol states studies should be at least 6 months in length
Volpe 1986	This trial is excluded because endometrial hyperplasia at baseline is not an exclusion criterion for entry into the trial (exclusion criterion for this review is any contraindication to HT). The numbers in each arm of the trial are small and the effects of treatment on the endometrium are evaluated by assessing the improvement in the endometrium from baseline as a result of treatment
Von Holst 2002	Nine months of therapy only.
Wahab 2002	This study is excluded because it is a 6 month non-randomised extension of a previous dose finding study
Wang 2006	The outcomes in this study are endometrial thickness by ultrasound and bleeding patterns only
Warming 2004a	Primary outcomes are bone related, secondary outcomes are bleeding. No data on endometrial hyperplasia
Weinstein 1990	No data in published paper on the number of endometrial biopsies performed at end of treatment in each treatment group. First author was contacted and reports that data no longer available

(*Continued*)

Wells 2002	This study is not a randomised controlled trial.
Williams 1990	Primary outcomes are vaginal spotting and adherence to therapy. No endometrial hyperplasia data reported
Yang 2001	Study only 4 months in length. Protocol states studies should be at least 6 months in length

Characteristics of studies awaiting assessment *[ordered by study ID]*

Pickar 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	Published abstract only. Letter sent to J Pickar 9 April 2008 requesting more details of the numbers of women randomised to each group

van de Weijer 2002

Methods	
Participants	
Interventions	
Outcomes	
Notes	Published abstract only

van der Mooren 1996

Methods	
Participants	
Interventions	
Outcomes	
Notes	Published abstract only. Letter sent to M van der Mooren on 9 April 2008 requesting more details about the methods and numbers of women in each group

Webster 1996

Methods	
Participants	
Interventions	
Outcomes	
Notes	Published abstract only.

DATA AND ANALYSES

Comparison 1. UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at 1 year	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Low dose estrogen	4	1499	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.84 [0.97, 8.29]
1.2 Moderate dose estrogen	5	1244	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.40 [5.47, 12.91]
1.3 High dose estrogen	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.69 [4.55, 25.10]
2 Cumulative endometrial hyperplasia at 18 - 24 months	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Low dose estrogen	6	893	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.42 [1.19, 4.92]
2.2 Moderate dose estrogen	6	627	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.86 [7.76, 18.14]
2.3 High dose estrogen	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	13.06 [5.88, 29.02]
3 Cumulative endometrial hyperplasia at 3 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Low dose estrogen	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Moderate dose estrogen	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	15.99 [9.28, 27.54]
3.3 High dose estrogen	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4 Endometrial Cancer 2-3 years	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Low dose estrogen	1	119	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.2 Moderate dose estrogen	2	357	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
4.3 High dose estrogen	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
5 Adherence to therapy at 1 year	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Moderate dose estrogen	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.12, 0.35]
6 Additional investigations (unscheduled biopsy)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Moderate dose estrogen	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.78 [6.97, 19.89]
7 Withdrawals due to adverse events	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Low dose estrogen	4	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.75, 1.90]
7.2 Moderate dose estrogen	3	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [2.02, 5.29]
7.3 High dose estrogen	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.09 [4.90, 20.80]

Comparison 2. ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at 1 year	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Low dose E + 0.2-0.5mg NETA (continuous)	2	461	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.06, 16.23]

1.2 Low dose E + 1 mg NETA (continuous)	2	455	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.48]
1.3 Low dose E + 1.5 mg MPA (continuous)	1	805	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.40 [0.23, 85.14]
1.4 Low dose E + 2.5 mg MPA (continuous)	1	534	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.5 Moderate dose E + 2.5mg MPA (continuous)	3	1010	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
1.6 Moderate dose E + 1 mg NETA (continuous)	2	388	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.59]
1.7 Moderate dose E + 0.5 mg NETA (continuous)	1	230	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
2 Cumulative endometrial hyperplasia at 2 years	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Low dose E + 0.2-0.5 mg NETA (continuous)	2	329	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.02, 2.34]
2.2 Low dose E + 1 mg NETA (continuous)	1	189	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Low dose E + 1.5mg MPA (continuous)	1	205	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.4 Low dose E + 2.5 MPA (continuous)	1	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.5 Low dose E + 1 mg drospirinone (continuous)	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.6 Low dose E + 2 mg drospirinone (continuous)	1	96	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.7 Low dose E + 3 mg drospirinone (continuous)	1	92	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.8 Low dose E + 25µg gestodene (continuous)	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.9 Moderate dose E + 1 mg NETA (continuous)	4	359	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.06]
2.10 Moderate dose E + 2.5mg MPA (continuous)	2	362	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.33 [0.15, 369.31]
3 Endometrial hyperplasia at 3 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Moderate dose E + 2.5mg MPA (continuous)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.05, 4.91]
4 Cumulative endometrial cancer at 2 years	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Low dose E + 25µg gestodene (continuous)	1	77	Odds Ratio (M-H, Fixed, 95% CI)	3.90 [0.15, 98.69]
4.2 Moderate dose E + 1mg NETA (continuous)	1	84	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Cumulative endometrial cancer at 3 years	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Moderate dose E + 2.5 mg MPA (continuous)	1	239	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
6 Cumulative endometrial cancer at 5+ years	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

6.1 Moderate dose E + 2.5 mg MPA (continuous)	1	16608	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.49, 1.39]
7 Adherence to therapy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Moderate dose E + 2.5mg MPA (continuous)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.69, 2.65]
8 Additional investigations (unscheduled biopsy)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.35, 2.25]
8.1 Moderate dose E + 2.5mg MPA (continuous)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.35, 2.25]
9 Withdrawals due to adverse events	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Low dose E + 0.25/0.5 mg NETA (continuous)	2	376	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.46, 1.66]
9.2 Low dose E + 1 mg NETA (continuous)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.60, 3.45]
9.3 Low dose E + 1mg drospirinone (continuous)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.45 [1.42, 8.42]
9.4 Low dose E + 2mg drospirinone (continuous)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.62, 5.06]
9.5 Low dose E +3 mg drospirinone (continuous)	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [0.80, 5.90]
9.6 Low dose E + 25µg gestodene (continuous)	1	111	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.80 [2.02, 16.65]
9.7 Moderate dose E + 0.5 mg NETA (continuous)	1	236	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.81 [1.35, 5.85]
9.8 Moderate dose E + 1 mg NETA (continuous)	4	534	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.05 [1.24, 3.39]

Comparison 3. ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at 1 year	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Moderate dose E (day 1-28) + 10mg MPA (day 1-12)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.45 [0.15, 375.57]
1.2 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.46, 118.84]
1.3 High dose E (day 1-21) + 10mg MPA (day 12-21)	1	49	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.09 [0.21, 21.13]
1.4 High dose E (day 1-84) + 10 mg MPA (day 71-84) - longcycle	1	52	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2 Cumulative endometrial hyperplasia at 2 years	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

2.1 Low dose E + 5 mg dydrogesterone (days 15-28)	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Low dose E + 10 mg dydrogesterone (days 15-28)	1	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Low dose E + 25µg gestodene (day 17-28)	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.4 Low dose E + 0.35mg NETA (days 4-6, 10-12, 16-18 ....)	1	57	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.5 Moderate dose E + 150µg desogestrel (days 13-24)	1	38	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.6 Moderate dose E (day 1-22) + 1mg NETA (day 13-22) + low dose E (day 23-28)	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.7 Moderate dose E (day 1-28) + 10mg MPA (day 1-12)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.65 [1.06, 54.98]
2.8 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.45 [0.77, 72.33]
2.9 Moderate dose E + 10 mg dydrogesterone (days 15-28)	1	151	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.10 Moderate dose E + 20 mg dydrogesterone (days 15-28)	1	159	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.11 Moderate dose E + 0.7mg NETA (days 4-6, 10-12, 16-18 ....)	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.12 Moderate dose E + 25µg gestodene (day 17-28)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.13 Moderate dose E + 50 µg gestodene (day 17-28)	1	73	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.14 High dose E (day 1-21) + 10mg MPA (day 12-21)	2	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.19 [0.42, 24.21]
2.15 High dose E (day 1-84) + 10 mg MPA (day 71-84) - longcycle	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.00, 8.12]
3 Cumulative endometrial hyperplasia at 3 years	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Low dose E (day 1-182) + 100 mg progesterone (day 168-182)	1	108	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.07, 18.20]
3.2 Moderate dose E (day 1-28) + 10 mg MPA (day 1-12)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.83 [0.69, 11.54]
3.3 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.78 [0.68, 11.34]
4 Cumulative endometrial cancer at 2 years	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Low dose E + 5 mg dydrogesterone (days 15-28)	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.10 [0.09, 285.72]

4.2 Low dose E + 10 mg dydrogesterone (days 15-28)	1	158	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.3 Low dose E + 25µg gestodene (day 17-28)	1	77	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.4 Moderate dose E + 10 mg dydrogesterone (days 15-28)	1	151	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.5 Moderate dose E + 20 mg dydrogesterone (days 15-28)	1	159	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.30 [0.31, 90.86]
4.6 Moderate dose E + 1 mg NETA (sequential)	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.7 Moderate dose E + 25µg gestodene (day 17-28)	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.8 Moderate dose E + 50 µg gestodene (day 17-28)	1	73	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.9 Moderate dose E (day 1-22) + 1mg NETA (day 13-22) + low dose E (day 23-28)	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
5 Cumulative endometrial cancer at 3 years	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Moderate dose E (day 1-28) +10 mg MPA (day 1-12)	1	237	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.27]
5.2 Moderate dose E (day 1-28) + 200mg progesterone(days 1-12)	1	239	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
6 Additional investigations (unscheduled biopsy)	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Low dose E (day 1-182) + 100 mg progesterone (day 168-182)	1	108	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.15 [0.43, 23.05]
6.2 Moderate dose E (day 1-28) +10 mg MPA (day 1-12)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [0.75, 3.81]
6.3 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.62, 3.33]
7 Withdrawal due to adverse events	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Low dose E + 5 mg dydrogesterone (days 15-28)	1	230	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.65, 3.10]
7.2 Low dose E + 10 mg dydrogesterone (days 15-28)	1	227	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.67, 3.19]
7.3 Low dose E + 25µg gestodene (day 17-28)	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.58 [2.46, 17.58]
7.4 Low dose E + 0.35mg NETA (days 4-6, 10-12, 16-18 ....)	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.41 [0.66, 8.85]
7.5 Moderate dose E + 50 µg desogestrel (days 12-21)	1	48	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.23, 3.58]
7.6 Moderate dose E + 10 mg dydrogesterone (days 15-28)	1	230	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.65, 3.10]

7.7 Moderate dose E + 20 mg dydrogesterone (days 15-28)	1	231	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.70 [0.80, 3.57]
7.8 Moderate dose E + 0.7mg NETA (days 4-6, 10-12, 16-18 ....)	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.68 [1.66, 13.22]
7.9 Moderate dose E (day 1-22) + 1mg NETA (day 13-22) + low dose E (day 23-28)	1	101	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.16 [0.80, 21.47]
7.10 Moderate dose E + 25µg gestodene (day 17-28)	1	111	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.07 [3.24, 20.12]
7.11 Moderate dose E + 50 µg gestodene (day 17-28)	1	112	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.85 [3.15, 19.56]
7.12 High dose E (day 1-21) + 10mg MPA (day 12-21)	2	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.58, 6.07]

Comparison 4. UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at one year	8		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Unopposed low dose E vs low dose E + 0.5 mg drospirinone	1	453	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.66 [1.89, 30.96]
1.2 Unopposed low dose E vs low dose E + 1 mg drospirinone	1	457	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.80 [1.93, 31.51]
1.3 Unopposed low dose E vs low dose E + 2 mg drospirinone	1	453	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.89 [1.31, 18.29]
1.4 Unopposed low dose E vs low dose E + 3 mg drospirinone	1	457	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.80 [1.93, 31.51]
1.5 Unopposed low dose E vs low dose E + 1.5 mg MPA	1	1092	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.82 [1.22, 11.90]
1.6 Unopposed low dose E vs low dose E + 2.5 mg MPA	1	821	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.55 [1.21, 17.08]
1.7 Unopposed low dose E vs low dose E + 0.1 mg NETA	1	496	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.98 [3.60, 13.52]
1.8 Unopposed low dose E vs low dose E + 0.2/0.25mg NETA	3	1065	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.90 [3.62, 13.15]
1.9 Unopposed low dose E vs low dose E + 0.5 mg NETA	2	816	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.41 [3.82, 14.38]
1.10 Unopposed low dose E vs low dose E + 1 mg NETA	2	559	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.72 [0.27, 122.11]
1.11 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA	3	1328	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.42 [5.63, 12.60]

1.12 Unopposed moderate dose E vs moderate dose E + 5 mg MPA	1	557	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.92 [5.16, 15.43]
1.13 Unopposed moderate dose E vs moderate dose E + 0.5 mg NETA	1	233	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.86 [3.75, 20.92]
1.14 Unopposed moderate dose E vs moderate dose E + 1 mg NETA	2	369	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.40 [4.55, 19.40]
2 Cumulative endometrial hyperplasia at 2 years	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Unopposed low dose E vs low dose E + 0.2 mg NETA	1	290	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.16, 9.83]
2.2 Unopposed low dose E vs low dose E + 0.5 mg NETA	1	278	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.57 [0.31, 40.95]
2.3 Unopposed low dose E vs low dose E + 1 mg NETA	1	286	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.70 [0.35, 38.81]
2.4 Unopposed low dose E vs low dose E + 1.5mg MPA	1	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.99 [2.83, 28.58]
2.5 Unopposed low dose E vs low dose E + 2.5mg MPA	1	196	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.94 [1.44, 16.95]
2.6 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA	2	356	Peto Odds Ratio (Peto, Fixed, 95% CI)	11.99 [7.09, 20.27]
2.7 Unopposed moderate dose E vs moderate dose E + 1 mg NETA	1	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	177.61 [36.08, 874.43]
3 Cumulative endometrial hyperplasia at 3 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Unopposed moderate dose E vs moderate dose E + 2.5mg MPA	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	17.07 [9.89, 29.44]
4 Endometrial cancer at one year	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Unopposed low dose E vs low dose E + 0.1 mg NETA	1	496	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.2 Unopposed low dose E vs low dose E + 0.2/0.25 mg NETA	1	498	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.3 Unopposed low dose E vs low dose E + 0.5 mg NETA	1	488	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.4 Unopposed moderate dose E vs moderate dose E + 2.5 MPA	1	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.29 [0.14, 367.19]
4.5 Unopposed moderate dose E vs moderate dose E + 5 MPA	1	557	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.16 [0.14, 360.91]
5 Endometrial cancer at 3 years	1	239	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.1 Unopposed moderate dose E vs moderate dose E +2.5mg MPA	1	239	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adherence to therapy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

6.1 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.10, 0.28]
7 Additional investigations (unscheduled biopsy)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Unopposed moderate dose E vs moderate dose E + 2.5 MPA	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	12.44 [7.36, 21.02]
8 Withdrawal due to adverse events	3	1909	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.85, 1.55]
8.1 Unopposed low dose E vs low dose E + 1.5 mg MPA (cont)	1	422	Odds Ratio (M-H, Fixed, 95% CI)	1.74 [0.78, 3.90]
8.2 Unopposed low dose E vs low dose E + 2.5 mg MPA (cont)	1	320	Odds Ratio (M-H, Fixed, 95% CI)	1.80 [0.64, 5.01]
8.3 Unopposed low dose E vs low dose E +0.25 mg NETA	1	230	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.37, 2.21]
8.4 Unopposed low dose E vs low dose E + 1 mg NETA	1	236	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.33, 1.88]
8.5 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA (cont)	1	224	Odds Ratio (M-H, Fixed, 95% CI)	5.21 [2.02, 13.41]
8.6 Unopposed moderate dose E vs moderate dose E + 0.5 mg NETA	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.26, 1.08]
8.7 Unopposed moderate dose E vs moderate dose E + 1 mg NETA	1	239	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.34, 1.49]

Comparison 5. UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at one year	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Unopposed low dose E vs low dose E + 30µg NGM (3days E only/ 3 days E+P)	1	525	Odds Ratio (M-H, Fixed, 95% CI)	5.91 [3.33, 10.47]
1.2 Unopposed low dose E vs low dose E + 90µg NGM (3days E only/ 3 days E+P)	1	507	Odds Ratio (M-H, Fixed, 95% CI)	188.68 [11.62, 3064.38]
1.3 Unopposed low dose E vs low dose E + 180 µg NGM (3 days E only/ 3 days E+P)	1	508	Odds Ratio (M-H, Fixed, 95% CI)	189.46 [11.67, 3076.98]
1.4 Unopposed moderate dose E vs moderate dose E + 5 mg MPA (11 days /cycle)	2	612	Odds Ratio (M-H, Fixed, 95% CI)	20.04 [7.16, 56.07]

1.5 Unopposed moderate dose E vs moderate dose E and 10 mg MPA (12 days/cycle)	2	792	Odds Ratio (M-H, Fixed, 95% CI)	67.46 [13.26, 343.08]
1.6 Unopposed moderate dose E vs moderate dose E + 10 mg progesterone (12days/cycle)	1	239	Odds Ratio (M-H, Fixed, 95% CI)	15.69 [3.62, 67.94]
1.7 Unopposed high dose E vs high dose E + 5 mg MPA (11days/cycle)	1	43	Odds Ratio (M-H, Fixed, 95% CI)	11.7 [2.19, 62.62]
2 Cumulative endometrial hyperplasia at 2 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Unopposed moderate dose E vs moderate dose E + 10 mg MPA (sequential)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.60 [5.32, 17.34]
2.2 Unopposed moderate dose E vs moderate dose E and 10 mg progesterone (sequential)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.50 [5.80, 19.01]
3 Cumulative endometrial hyperplasia at 3 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Unopposed moderate dose E vs moderate dose E + 10 mg MPA (sequential)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	12.71 [7.43, 21.76]
3.2 Unopposed moderate dose vs moderate dose E and 10 mg progesterone (sequential)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	12.90 [7.55, 22.05]
4 Endometrial cancer at one year	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Unopposed moderate dose E vs moderate dose E + 5 mg MPA (sequential)	1	560	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.23 [0.14, 364.65]
4.2 Unopposed moderate dose E vs moderate dose E and 10 mg MPA (sequential)	1	555	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.06, 15.41]
5 Endometrial cancer at 3 years	1	476	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.1 Unopposed moderate dose E vs moderate dose E and 10 mg MPA (sequential)	1	237	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Unopposed moderate dose E vs moderate dose E + 10 mg progesterone (sequential)	1	239	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Adherence to therapy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Unopposed moderate dose E vs moderate dose E and 10 mg MPA (sequential)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.12, 0.34]
6.2 Unopposed moderate dose E vs moderate dose E + 10 mg progesterone (sequential)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.13, 0.36]
7 Additional investigations (endometrial biopsy)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Unopposed moderate dose E vs moderate dose E + 10 mg MPA (sequential)	1	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.94 [5.32, 15.01]

7.2 Unopposed moderate dose E vs moderate dose E and 10 mg progesterone (sequential)	1	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.90 [5.89, 16.63]
8 Withdrawal due to adverse events	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Unopposed low dose E vs low dose E + 30µg NGM (3days E only/ 3 days E+P)	1	624	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.71 [1.64, 4.48]
8.2 Unopposed low dose E vs low dose E + 90µg NGM (3days E only/ 3 days E+P)	1	624	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.28 [1.39, 3.72]
8.3 Unopposed low dose E vs low dose E + 180µg NGM (3days E only/ 3 days E+P)	1	627	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.22, 3.17]
8.4 Unopposed moderate dose E vs moderate dose E + 5 mg MPA (sequential)	1	83	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.17, 2.31]
8.5 Unopposed high dose E vs high dose E + 5 mg MPA (sequential)	1	90	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.10, 0.83]

Comparison 6. ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at 1 year	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 14-25)	1	18	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 15-28)	1	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.11, 3.85]
1.3 Moderate dose E + 5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 14-25)	1	19	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.4 Moderate dose E +5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 15-28)	1	546	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.5 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.71]
1.6 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)	1	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.16]

1.7 Moderate dose E + 1 mg NETA (cont) vs low dose E + 90µg NGM (days 4-6, 10-12 ....)	1	361	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.8 Moderate dose E + 1 mg NETA (cont) vs low dose E + 180µg NGM (days 4-6, 10-12 ....)	1	295	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2 Cumulative endometrial hyperplasia at 2 years	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.35 mg NETA (day 4-6, 10-12 ...)	1	62	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.7 mg NETA (day 4-6, 10-12 ...)	1	56	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 1mg NETA (days 13-22)	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.4 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.05, 1.70]
2.5 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)	1	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.05, 2.61]
2.6 Moderate dose E + 1 mg NETA (cont) vs low dose E + 90µg NGM (days 4-6, 10-12 ....)	1	282	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3 Cumulative endometrial hyperplasia at 3 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.05, 1.02]
3.2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)	1	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.05, 1.04]
4 Endometrial cancer at 1 year	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E+ 5 mg MPA (day 15-28)	1	556	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.2 Moderate dose E + 5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 15-28)	1	546	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.77]
5 Cumulative endometrial cancer at 2 years	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

5.1 Low dose E + 25 µg gestodene (cont) vs Low dose E + 25 µg gestodene (day 17-28)	1	68	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
5.2 Low dose E + 25 µg gestodene (cont) vs moderate dose E + 25 µg gestodene (day 17-28)	1	61	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.01 [0.12, 311.10]
5.3 Low dose E + 25 µg gestodene (cont) vs moderate dose E + 50 µg gestodene (day 17-28)	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.57 [0.13, 333.61]
5.4 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 1mg NETA (days 13-23)	1	84	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
6 Cumulative endometrial cancer at 3 years	1	478	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)	1	238	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)	1	240	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adherence to therapy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.66, 2.55]
7.2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)	1	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [0.73, 2.74]
8 Additional Investigations	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.22, 1.22]
8.2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)	1	240	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.25, 1.48]
9 Withdrawal due to adverse events	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Moderate dose E + 1 mg NETA (cont) vs low dose E + 90 µg NGM (days 4-6, 10-12 ....)	1	438	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.46, 1.47]
9.2 Moderate dose E + 1 mg NETA (cont) vs low dose E + 180 µg NGM (days 4-6, 10-12 ....)	1	434	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.14, 0.38]

9.3 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.35 mg NETA (day 4-6, 10-12 ...)	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.61, 4.91]
9.4 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.7 mg NETA (day 4-6, 10-12 ...)	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.61, 4.91]
9.5 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 14-25)	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.4 [0.06, 2.77]
9.6 Moderate dose E + 5mg MPA (cont) vs moderate dose E+ 5mg MPA (day 14-25)	1	24	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.95]
9.7 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 1mg NETA (days 13-23)	1	100	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.35, 4.32]

Comparison 7. CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at 1 year	16		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Low dose E + 0.5 mg DRSP vs low dose E + 1mg DRSP	1	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.2 Low dose E +2 mg DRSP vs Low dose E + 3 mg DRSP	1	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.52 [0.15, 379.06]
1.3 Low dose E + 0.125 mg TMG vs low dose E + 0.5 mg NETA	1	241	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.4 Low dose E + 0.1 to 0.25 mg NETA vs low dose E + 0.5 mg NETA	1	741	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [0.17, 11.48]
1.5 Low dose E + 0.2 - 0.5 mg NETA vs Low dose E + 1 mg NETA	2	683	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.75 [0.15, 391.13]
1.6 Low dose E + 1.5 mg MPA vs low dose E + 2.5 mg MPA	1	817	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.50 [0.24, 85.08]
1.7 Low dose E + 0.25 - 0.5 mg NETA vs moderate dose E + 1 mg NETA	2	193	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.8 Low dose E + 0.5 mg NETA vs moderate dose E + 2.5 mg MPA	1	72	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

1.9 Low dose E + 1 mg NETA vs low dose E +2.5 mg MPA	1	357	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.10 Low dose E + 1.5 mg MPA vs mod dose E + 2.5 mg MPA	1	822	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.54 [0.24, 85.12]
1.11 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA	1	551	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.12 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA	1	53	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.13 Low dose E + 1 mg NETA vs moderate dose E + 1 mg NETA	1	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.14 Moderate dose E + 0.5 mg NETA vs moderate dose E + 2.5 mg MEGA	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.15 Moderate dose E + 0.5 mg NETA vs moderate dose E + 2.5 mg MPA	1	232	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.16 Moderate dose E + 1 mg NETA vs moderate dose E + 5 mg MEGA	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.17 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA	2	861	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.28 [0.45, 116.76]
1.18 Moderate dose E + 5 mg MPA vs moderate dose E + 10 mg MPA	1	305	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.19 Mod - high dose E + 2.5 mg MPA vs mod - high dose E + 1 mg NETA	1	287	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.20 Mod - high dose E + 5 mg MPA vs mod - high dose E + 1 mg NETA	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.21 High dose E + 2 mg DNG vs moderate dose E + 1 mg NETA	1	277	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.22 High dose E + 3 mg DNG vs moderate dose E + 1 mg NETA	1	255	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2 Cumulative endometrial hyperplasia at 2 years	10		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Low dose E + 1 mg DRSP vs low dose E + 2 mg DRSP	1	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Low dose E + 2mg DRSP vs low dose E + 3 mg DRSP	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Low dose E + 0.125 mg TMG vs moderate dose E + 1 mg NETA	1	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

2.4 Low dose E + 0.2 - 0.5mg NETA vs Low dose E + 1 mg NETA	1	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.5 Low dose E + 1.5 mg MPA vs low dose E + 2.5 mg MPA	1	210	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.6 Low dose E + 2 mg MPA vs moderate dose E + 2mg MPA	1	142	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.28]
2.7 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA	1	128	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.8 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA	1	53	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.9 Low dose E + 1.5 mg MPA vs moderate dose E + 2.5 mg MPA	1	206	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.10 Low dose E + 1 mg NETA vs moderate dose E + 1 mg NETA	1	136	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.11 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA	3	427	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.12 Moderate dose E + 5 mg MPA vs moderate dose E + 10 mg MPA	2	287	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.13 Moderate to high dose E + 5 mg MPA vs high dose E + 1 mg NETA	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.14 Moderate to high dose E + 2.5 mg MPA vs high dose E + 1 mg NETA	1	173	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.15 Moderate to high dose E + 2.5 mg MPA vs moderate to high dose E + 5 mg MPA	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.16 High dose E + 2.5 mg MPA vs high dose E + 5 mg MPA	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3 Endometrial cancer at one year	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Low dose E + 0.1 to 0.25 mg NETA vs low dose E + 0.5 mg NETA	1	741	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA	1	553	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4 Withdrawal due to adverse events	9		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Low dose E + 0.5 mg DRSP vs low dose E + 1mg DRSP	1	458	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.48, 1.39]

4.2 Low dose E +2 mg DRSP vs low dose E + 3 mg DRSP	2	578	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.72, 1.75]
4.3 Low dose E + 1 mg DRSP vs low dose E + 2 mg DRSP	1	120	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.09 [0.90, 4.86]
4.4 Low dose E + 0.2 - 0.5 mg NETA vs moderate dose E + 1 mg NETA	2	619	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.69, 1.72]
4.5 Low dose E + 0.25 - 0.5 mg NETA vs moderate dose E + 1 mg NETA	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.27, 7.05]
4.6 Low dose E + 1 mg NETA vs Low dose E + 2.5 MPA	1	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.52, 1.88]
4.7 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA	1	59	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.10, 2.88]
4.8 Moderate dose E + 0.5 mg NETA vs moderate dose E + 2.5 mg MPA	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [0.82, 3.18]
4.9 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA	2	518	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.51, 1.46]
4.10 Moderate dose E + 5 mg MPA vs moderate dose E + 10 mg MPA	1	378	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [0.91, 3.36]
4.11 Moderate to high dose E + 2.5 mg MPA vs moderate to high dose E + 5 mg MPA	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.62, 3.58]
4.12 High dose E + 2.5 mg MPA vs high dose E + 5 mg MPA	1	140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.76 [0.75, 4.10]

Comparison 8. SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Endometrial hyperplasia at 1 year	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Low dose E + 5mg dydrogesterone (d 15-28) vs low dose E + 10mg dydrogesterone (d15-28)	1	124	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.18 [0.16, 414.15]
1.2 Low dose E + 0.125 mg TMG (d15-28) vs low dose E + 0.25 mg TMG (d15-28)	1	544	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.12, 4.06]
1.3 Low dose E + 0.125 - 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d15-28)	1	801	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [0.37, 11.38]

1.4 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 0.5 mg TMG (d15-28)	1	244	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.5 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)	1	243	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.6 Moderate dose E + 0.5 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)	1	235	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.7 Moderate dose E + 0.5mg TMG (d15-28) vs moderate dose E + 0.5mg norgestrel (d19-28)	1	396	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.19, 2.61]
1.8 Moderate dose E + 5 mg MPA (d12 -25) vs Moderate dose E + 10 mg MPA (d12-25)	2	717	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.43 [1.09, 37.85]
1.9 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.05, 5.04]
1.10 Moderate dose E + 25µg gestodene (d17-28) vs moderate dose E + 50µg gestodene (d17-28)	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.11 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/month)	1	195	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.70 [1.93, 39.27]
1.12 Moderate dose E + 10 mg MPA (14d/3mth) vs moderate dose E +10 mg MPA (14 d/month)	1	41	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.95 [0.11, 308.59]
1.13 High dose E + 10 mg MPA (10d/3mth) vs high dose E + 10 mg MPA (10d/mth)	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 2.33]
1.14 Moderate dose E + 10 mg MPA (14d/3mth) vs moderate dose E + 10 mg MPA (28d/3mth)	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.05, 15.09]
1.15 High dose E + 10 mg MPA (triphasic) vs high dose E + 10 mg MPA (biphasic)	1	393	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.21 [0.14, 363.26]
1.16 High dose E + 10 mg MPA (triphasic) vs high dose E + 1 mg NETA (triphasic)	1	340	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2 Cumulative endometrial hyperplasia at 2 years	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

2.1 Low dose E + 0.35mg NETA (d 4-6, 10-12 ....) vs Moderate dose E + 0.7mg NETA (d 4-6, 10-12 ....)	1	58	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 Low dose E + 5mg DYG (d15-28) vs low dose E + 10 mg DYG (d15-28)	1	195	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.3 Moderate dose E + 10mg DYG (d15-28) vs moderate dose E + 20 mg DYG (d15-28)	1	184	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.4 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.30, 6.12]
2.5 High dose E + 10 mg MPA (10d/3mths) vs high dose E +10 mg MPA (10d/mth)	1	44	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 1.37]
2.6 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/mth)	1	195	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.24 [1.27, 21.51]
3 Cumulative endometrial hyperplasia at 3 years	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.32, 3.24]
3.2 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/mth)	1	195	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.64 [2.03, 15.65]
4 Endometrial cancer at one year	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Low dose E + 0.125 mg TMG (d15-28) vs low dose E + 0.25 mg TMG (d15-28)	1	544	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.2 Low dose E + 0.125 - 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d15-28)	1	801	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.3 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 0.5 mg TMG (d15-28)	1	244	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.4 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)	1	243	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.33]
4.5 Moderate dose E + 0.5 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)	1	235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.76]

4.6 Moderate dose E + 0.5mg TMG (d15-28) vs moderate dose E + 0.5mg norgestrel (d19-28)	1	396	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 5.98]
4.7 Moderate dose E + 5 mg MPA (d12 -25) vs Moderate dose E + 10 mg MPA (d12-25)	2	717	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
5 Cumulative endometrial cancer at 2 years	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Low dose E + 25µg gestodene vs moderate dose E + 25 µg gestodene	1	61	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Low dose E + 5mg DYG (d15-28) vs low dose E + 10 mg DYG (d15-28)	1	195	Odds Ratio (M-H, Fixed, 95% CI)	2.88 [0.12, 71.56]
5.3 Moderate dose E + 10mg DYG (d15-28) vs moderate dose E + 20 mg DYG (d15-28)	1	184	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.51]
5.4 Moderate dose E + 25ug gestodene vs moderate dose E + 50ug gestodene	1	57	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Cumulative endometrial cancer at 3 years	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)	1	238	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/mth)	1	195	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.13, 82.62]
7 Adherence to therapy	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)	1	238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.57, 2.07]
7.2 High dose E + 10 mg MPA (triphasic) vs high dose E + 10 mg MPA (biphasic)	1	393	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.50 [0.79, 2.87]
8 Additional Investigations	1	238	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.55, 2.56]
8.1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)	1	238	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.55, 2.56]
9 Withdrawals due to adverse events	6		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Low dose E + 0.35mg NETA (d 4-6, 10-12 ....) vs Moderate dose E + 0.7mg NETA (d 4-6, 10-12 ....)	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.17, 1.13]

9.2 Low dose E + 5mg DYG (d15-28) vs low dose E + 10 mg DYG (d15-28)	1	231	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.47, 2.01]
9.3 Moderate dose E + 10mg DYG (d15-28) vs moderate dose E + 20 mg DYG (d15-28)	1	235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.41, 1.68]
9.4 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 0.5 mg TMG (d15-28)	1	276	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.48, 1.56]
9.5 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)	1	278	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.44, 1.38]
9.6 Moderate dose E + 0.5 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)	1	272	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.51, 1.59]
9.7 Moderate dose E + 0.5mg TMG (d15-28) vs moderate dose E + 0.5mg norgestrel (d19-28)	1	634	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.84, 2.08]
9.8 High dose E + 10 mg MPA (10d/3mth) vs high dose E +10 mg MPA (10d/mth)	1	52	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.08, 1.83]
9.9 High dose E + 10 mg MPA (triphasic) vs high dose E + 10 mg MPA (biphasic)	1	393	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.37, 1.83]
9.10 High dose E + 10 mg MPA (triphasic) vs high dose E + 1 mg NETA (triphasic)	1	340	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.40 [0.78, 2.52]

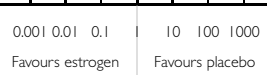
Analysis 1.1. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 1 Endometrial hyperplasia at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 1 Endometrial hyperplasia at 1 year

Study or subgroup	Estrogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose estrogen					
CHART 1996	1/259	0/83		5.5 %	3.75 [0.04, 362.22]
HOPE 2001	10/548	0/261		64.7 %	4.45 [1.17, 16.88]
Notelovitz 1997	1/59	1/60		14.8 %	1.02 [0.06, 16.46]
Portman 2003	1/114	1/115		14.9 %	1.01 [0.06, 16.23]
Subtotal (95% CI)	**980**	**519**		**100.0 %**	**2.84 [0.97, 8.29]**
Total events: 13 (Estrogen), 2 (Placebo)					
Heterogeneity: Chi² = 1.51, df = 3 (P = 0.68); I² =0.0%					
Test for overall effect: Z = 1.91 (P = 0.057)					
2 Moderate dose estrogen					
CHART 1996	9/61	0/83		10.0 %	12.19 [3.13, 47.53]
HOPE 2001	20/249	0/261		23.1 %	8.39 [3.43, 20.52]
Notelovitz 1997	12/59	1/60		14.0 %	6.70 [2.13, 21.11]
PEPI 1995	25/119	0/119		27.0 %	9.26 [4.05, 21.16]
Portman 2003	23/118	1/115		25.9 %	7.44 [3.20, 17.29]
Subtotal (95% CI)	**606**	**638**		**100.0 %**	**8.40 [5.47, 12.91]**
Total events: 89 (Estrogen), 2 (Placebo)					
Heterogeneity: Chi² = 0.57, df = 4 (P = 0.97); I² =0.0%					
Test for overall effect: Z = 9.71 (P < 0.00001)					
3 High dose estrogen					
Notelovitz 1997	26/60	1/60		100.0 %	10.69 [4.55, 25.10]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**10.69 [4.55, 25.10]**
Total events: 26 (Estrogen), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.44 (P < 0.00001)					

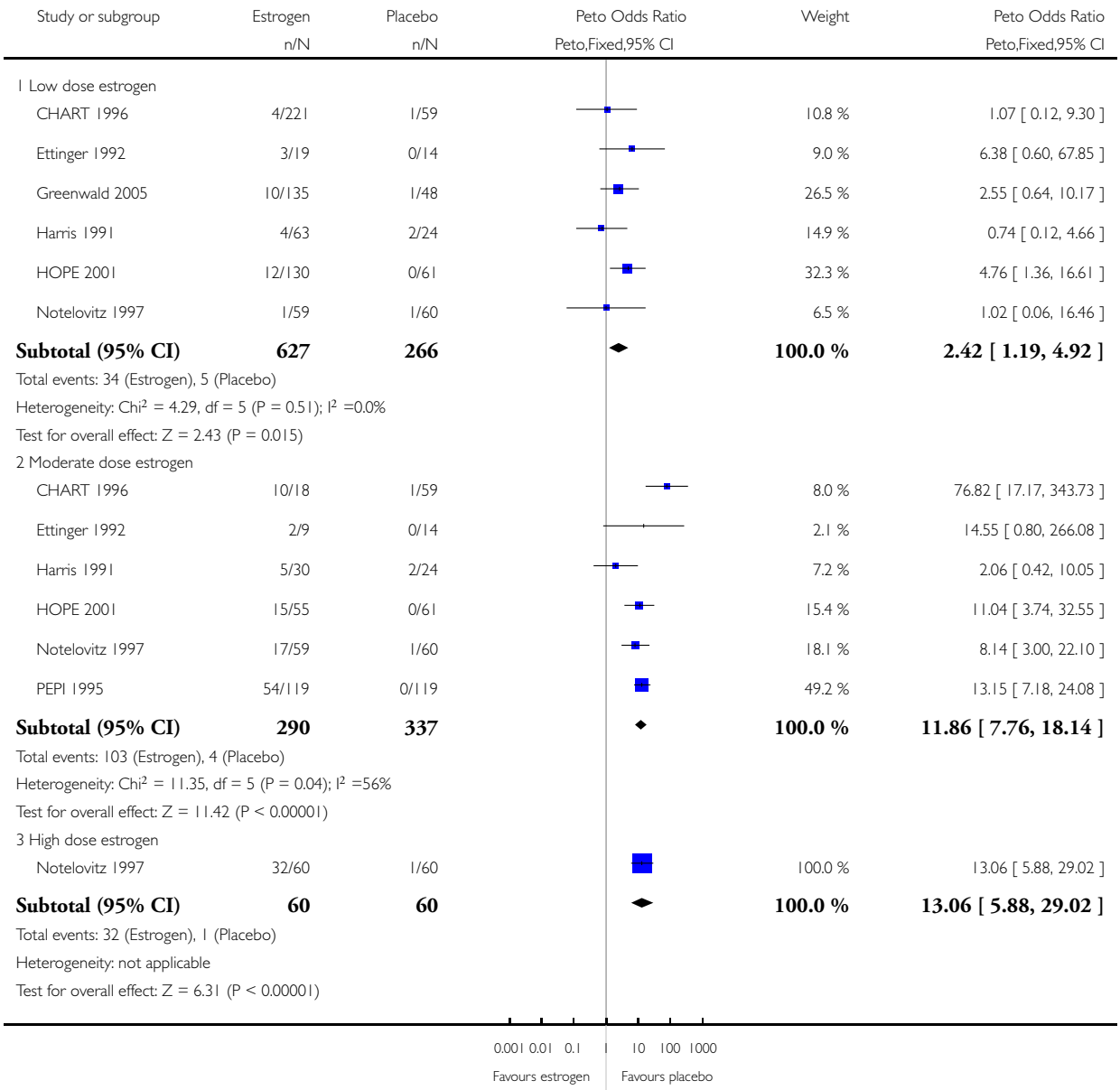


Analysis 1.2. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 2 Cumulative endometrial hyperplasia at 18 - 24 months.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 2 Cumulative endometrial hyperplasia at 18 - 24 months



Analysis 1.3. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 3 Cumulative endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 3 Cumulative endometrial hyperplasia at 3 years

Study or subgroup	Estrogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose estrogen					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Moderate dose estrogen					
PEPI 1995	74/119	2/119		100.0 %	15.99 [9.28, 27.54]
Subtotal (95% CI)	**119**	**119**		**100.0 %**	**15.99 [9.28, 27.54]**
Total events: 74 (Estrogen), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.99 (P < 0.00001)					
3 High dose estrogen					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 4 Endometrial Cancer 2-3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 4 Endometrial Cancer 2-3 years

Study or subgroup	Estrogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose estrogen				
Notelovitz 1997	0/59	0/60		0.0 [0.0, 0.0]
Subtotal (95% CI)	**59**	**60**		**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose estrogen				
Notelovitz 1997	0/59	0/60		0.0 [0.0, 0.0]
PEPI 1995	0/119	1/119		0.14 [0.00, 6.82]
Subtotal (95% CI)	**178**	**179**		**0.14 [0.00, 6.82]**
Total events: 0 (Estrogen), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
3 High dose estrogen				
Notelovitz 1997	0/60	0/60		0.0 [0.0, 0.0]
Subtotal (95% CI)	**60**	**60**		**0.0 [0.0, 0.0]**
Total events: 0 (Estrogen), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

Analysis 1.5. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 5 Adherence to therapy at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 5 Adherence to therapy at 1 year

Study or subgroup	Estrogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose estrogen					
PEPI 1995	52/119	96/119		100.0 %	0.21 [0.12, 0.35]
Subtotal (95% CI)	**119**	**119**		**100.0 %**	**0.21 [0.12, 0.35]**
Total events: 52 (Estrogen), 96 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.87 (P < 0.00001)					
Test for subgroup differences: Not applicable					

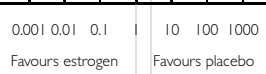
Analysis 1.6. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 6 Additional investigations (unscheduled biopsy).

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 6 Additional investigations (unscheduled biopsy)

Study or subgroup	Estrogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose estrogen					
PEPI 1995	79/119	10/119		100.0 %	11.78 [6.97, 19.89]
Subtotal (95% CI)	**119**	**119**		**100.0 %**	**11.78 [6.97, 19.89]**
Total events: 79 (Estrogen), 10 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.22 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 1.7. Comparison 1 UNOPPOSED ESTROGEN VERSUS PLACEBO, Outcome 7 Withdrawals due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 1 UNOPPOSED ESTROGEN VERSUS PLACEBO

Outcome: 7 Withdrawals due to adverse events

Study or subgroup	Estrogen n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose estrogen					
Greenwald 2005	31/135	11/48		35.1 %	1.00 [0.46, 2.19]
HOPE 2001	17/212	3/103		23.1 %	2.35 [0.90, 6.17]
Notelovitz 1997	6/59	8/60		17.4 %	0.74 [0.24, 2.24]
Portman 2003	10/115	9/117		24.4 %	1.14 [0.45, 2.91]
Subtotal (95% CI)	**521**	**328**		**100.0 %**	**1.20 [0.75, 1.90]**
Total events: 64 (Estrogen), 31 (Placebo)					
Heterogeneity: Chi^2 = 2.82, df = 3 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					
2 Moderate dose estrogen					
HOPE 2001	22/103	3/103		33.4 %	5.59 [2.43, 12.88]
Notelovitz 1997	23/59	8/60		35.0 %	3.74 [1.66, 8.46]
Portman 2003	14/119	9/117		31.6 %	1.59 [0.67, 3.74]
Subtotal (95% CI)	**281**	**280**		**100.0 %**	**3.26 [2.02, 5.29]**
Total events: 59 (Estrogen), 20 (Placebo)					
Heterogeneity: Chi^2 = 4.43, df = 2 (P = 0.11); I^2 =55%					
Test for overall effect: Z = 4.81 (P < 0.00001)					
3 High dose estrogen					
Notelovitz 1997	42/60	8/60		100.0 %	10.09 [4.90, 20.80]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**10.09 [4.90, 20.80]**
Total events: 42 (Estrogen), 8 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.27 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 25.21, df = 2 (P = 0.00), I^2 =92%					

Analysis 2.1. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 1 Endometrial hyperplasia at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 1 Endometrial hyperplasia at 1 year

Study or subgroup	cont E+P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.2-0.5mg NETA (continuous)				
CHART 1996	0/149	0/83		0.0 [0.0, 0.0]
Portman 2003	1/114	1/115		1.01 [0.06, 16.23]
Subtotal (95% CI)	**263**	**198**		**1.01 [0.06, 16.23]**
Total events: 1 (cont E+P), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.01 (P = 1.0)				
2 Low dose E + 1 mg NETA (continuous)				
CHART 1996	0/136	0/83		0.0 [0.0, 0.0]
Portman 2003	0/121	1/115		0.13 [0.00, 6.48]
Subtotal (95% CI)	**257**	**198**		**0.13 [0.00, 6.48]**
Total events: 0 (cont E+P), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.03 (P = 0.31)				
3 Low dose E + 1.5 mg MPA (continuous)				
HOPE 2001	2/544	0/261		4.40 [0.23, 85.14]
Subtotal (95% CI)	**544**	**261**		**4.40 [0.23, 85.14]**
Total events: 2 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.98 (P = 0.33)				
4 Low dose E + 2.5 mg MPA (continuous)				
HOPE 2001	0/273	0/261		0.0 [0.0, 0.0]
Subtotal (95% CI)	**273**	**261**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
5 Moderate dose E + 2.5mg MPA (continuous)				
HOPE 2001	0/278	0/261		0.0 [0.0, 0.0]
PEPI 1995	0/120	0/119		0.0 [0.0, 0.0]
Portman 2003	0/117	1/115		0.13 [0.00, 6.70]
Subtotal (95% CI)	**515**	**495**		**0.13 [0.00, 6.70]**

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Study or subgroup	cont E+P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 0 (cont E+P), 1 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.01 (P = 0.31)				
6 Moderate dose E + 1 mg NETA (continuous)				
CHART 1996	0/71	0/83		0.0 [0.0, 0.0]
Portman 2003	0/119	1/115		0.13 [0.00, 6.59]
Subtotal (95% CI)	**190**	**198**		**0.13 [0.00, 6.59]**
Total events: 0 (cont E+P), 1 (Placebo)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.02 (P = 0.31)				
7 Moderate dose E + 0.5 mg NETA (continuous)				
Portman 2003	0/115	1/115		0.14 [0.00, 6.82]
Subtotal (95% CI)	**115**	**115**		**0.14 [0.00, 6.82]**
Total events: 0 (cont E+P), 1 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
Test for subgroup differences: Chi² = 4.09, df = 5 (P = 0.54), I² =0.0%				

Analysis 2.2. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 2 Cumulative endometrial hyperplasia at 2 years

Study or subgroup	cont E+P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.2-0.5 mg NETA (continuous)				
CHART 1996	1/126	1/59		0.43 [0.02, 8.53]
Greenwald 2005	0/96	1/48		0.05 [0.00, 3.18]
Subtotal (95% CI)	**222**	**107**		**0.21 [0.02, 2.34]**
Total events: 1 (cont E+P), 2 (Placebo)				
Heterogeneity: Chi^2 = 0.69, df = 1 (P = 0.41); I^2 =0.0%				
Test for overall effect: Z = 1.27 (P = 0.20)				
2 Low dose E + 1 mg NETA (continuous)				
CHART 1996	0/130	1/59		0.04 [0.00, 2.79]
Subtotal (95% CI)	**130**	**59**		**0.04 [0.00, 2.79]**
Total events: 0 (cont E+P), 1 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.48 (P = 0.14)				
3 Low dose E + 1.5mg MPA (continuous)				
HOPE 2001	0/144	0/61		0.0 [0.0, 0.0]
Subtotal (95% CI)	**144**	**61**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Low dose E + 2.5 MPA (continuous)				
HOPE 2001	0/66	0/61		0.0 [0.0, 0.0]
Subtotal (95% CI)	**66**	**61**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
5 Low dose E + 1 mg drospirinone (continuous)				
Warming 2004	0/39	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**39**	**47**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
6 Low dose E + 2 mg drospirinone (continuous)				
Warming 2004	0/49	0/47		0.0 [0.0, 0.0]

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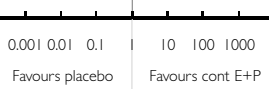
Study or subgroup	cont E+P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**49**	**47**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
7 Low dose E + 3 mg drospirinone (continuous)				
Warming 2004	0/45	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**45**	**47**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
8 Low dose E + 25g gestodene (continuous)				
Byrjalsen 1999	0/34	0/43		0.0 [0.0, 0.0]
Subtotal (95% CI)	**34**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
9 Moderate dose E + 1 mg NETA (continuous)				
Byrjalsen 2000	0/30	0/25		0.0 [0.0, 0.0]
CHART 1996	0/65	1/59		0.12 [0.00, 6.19]
Greenwald 2005	0/48	1/48		0.14 [0.00, 6.82]
Obel 1993	0/39	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**182**	**177**		**0.13 [0.01, 2.06]**
Total events: 0 (cont E+P), 2 (Placebo)				
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%				
Test for overall effect: Z = 1.45 (P = 0.15)				
10 Moderate dose E + 2.5mg MPA (continuous)				
HOPE 2001	0/62	0/61		0.0 [0.0, 0.0]
PEPI 1995	1/120	0/119		7.33 [0.15, 369.31]
Subtotal (95% CI)	**182**	**180**		**7.33 [0.15, 369.31]**
Total events: 1 (cont E+P), 0 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
Test for subgroup differences: Chi^2 = 3.80, df = 3 (P = 0.28), I^2 =21%				

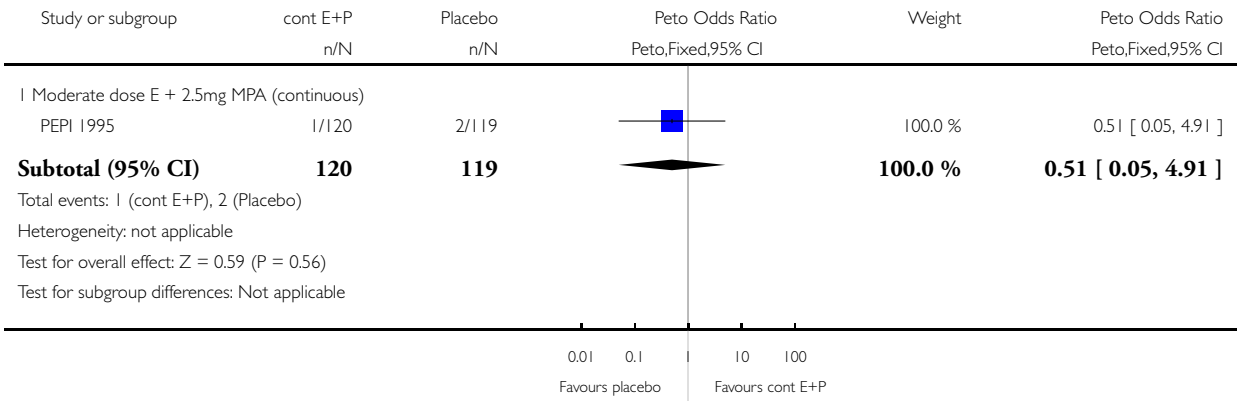


Analysis 2.3. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 3 Endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 3 Endometrial hyperplasia at 3 years



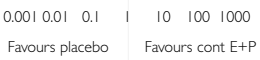
Analysis 2.4. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 4 Cumulative endometrial cancer at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 4 Cumulative endometrial cancer at 2 years

Study or subgroup	cont E+P n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Low dose E + 25g gestodene (continuous)				
Byrjalsen 1999	1/34	0/43		3.90 [0.15, 98.69]
Subtotal (95% CI)	**34**	**43**		**3.90 [0.15, 98.69]**
Total events: 1 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.82 (P = 0.41)				
2 Moderate dose E + 1mg NETA (continuous)				
Obel 1993	0/39	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**39**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (cont E+P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				



Analysis 2.5. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 5 Cumulative endometrial cancer at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 5 Cumulative endometrial cancer at 3 years

Study or subgroup	cont E+P n/N	placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E + 2.5 mg MPA (continuous)					
PEPI 1995	0/120	1/119		100.0 %	0.33 [0.01, 8.13]
Subtotal (95% CI)	**120**	**119**		**100.0 %**	**0.33 [0.01, 8.13]**
Total events: 0 (cont E+P), 1 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					

Analysis 2.6. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 6 Cumulative endometrial cancer at 5+ years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 6 Cumulative endometrial cancer at 5+ years

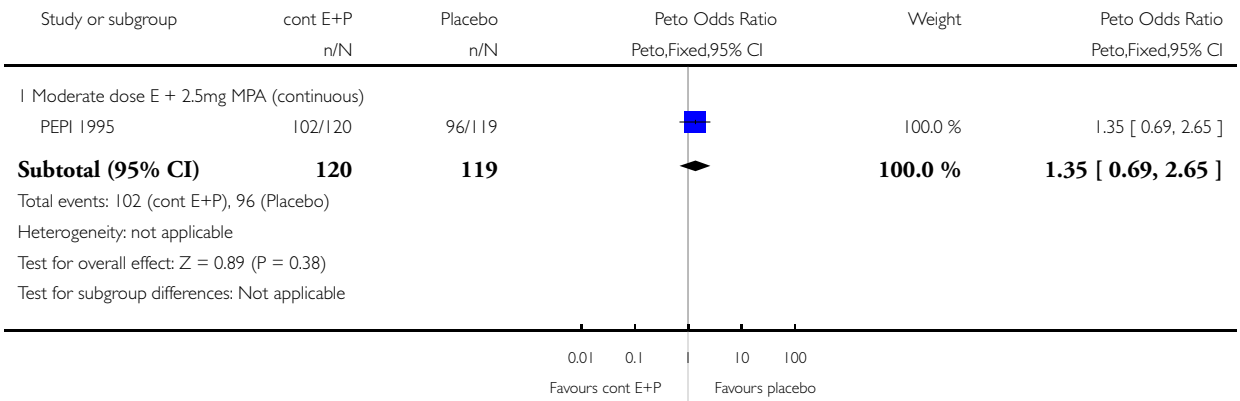
Study or subgroup	cont E + P n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E + 2.5 mg MPA (continuous)					
WHI 2002	27/8506	31/8102		100.0 %	0.83 [0.49, 1.39]
Subtotal (95% CI)	**8506**	**8102**		**100.0 %**	**0.83 [0.49, 1.39]**
Total events: 27 (cont E + P), 31 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					

Analysis 2.7. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 7 Adherence to therapy.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 7 Adherence to therapy

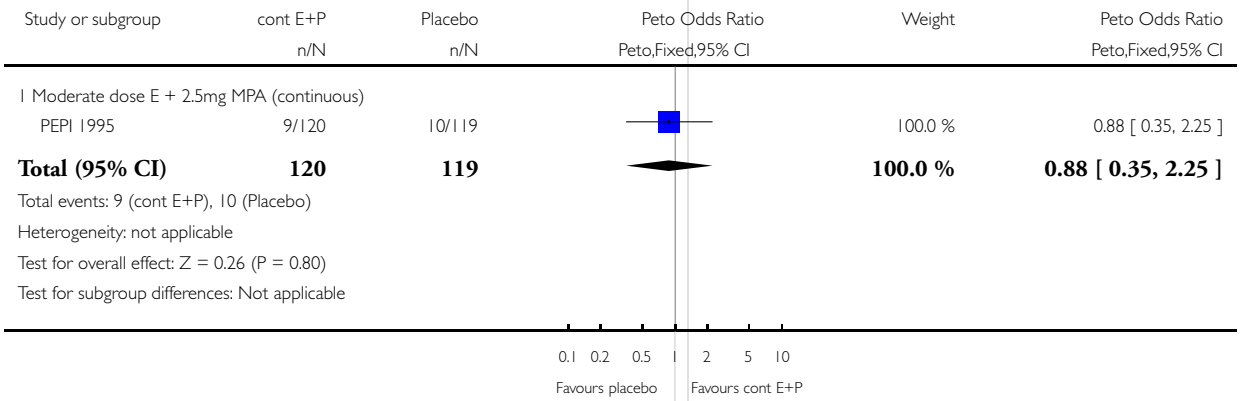


Analysis 2.8. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 8 Additional investigations (unscheduled biopsy).

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 8 Additional investigations (unscheduled biopsy)



Analysis 2.9. Comparison 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO, Outcome 9 Withdrawals due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 2 ESTROGEN + PROGESTOGEN (continuous) VS PLACEBO

Outcome: 9 Withdrawals due to adverse events

Study or subgroup	cont E+P n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.25/0.5 mg NETA (continuous)					
Greenwald 2005	15/96	11/48		51.0 %	0.61 [0.25, 1.50]
Portman 2003	11/115	9/117		49.0 %	1.27 [0.51, 3.16]
Subtotal (95% CI)	**211**	**165**		**100.0 %**	**0.88 [0.46, 1.66]**
Total events: 26 (cont E+P), 20 (placebo)					
Heterogeneity: Chi^2 = 1.23, df = 1 (P = 0.27); I^2 =19%					
Test for overall effect: Z = 0.41 (P = 0.68)					
2 Low dose E + 1 mg NETA (continuous)					
Portman 2003	13/121	9/117		100.0 %	1.44 [0.60, 3.45]
Subtotal (95% CI)	**121**	**117**		**100.0 %**	**1.44 [0.60, 3.45]**
Total events: 13 (cont E+P), 9 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.81 (P = 0.42)					
3 Low dose E + 1mg drospirinone (continuous)					
Warming 2004	18/60	6/60		100.0 %	3.45 [1.42, 8.42]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**3.45 [1.42, 8.42]**
Total events: 18 (cont E+P), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0064)					
4 Low dose E + 2mg drospirinone (continuous)					
Warming 2004	10/60	6/60		100.0 %	1.77 [0.62, 5.06]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**1.77 [0.62, 5.06]**
Total events: 10 (cont E+P), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
5 Low dose E +3 mg drospirinone (continuous)					
Warming 2004	12/60	6/60		100.0 %	2.18 [0.80, 5.90]
Subtotal (95% CI)	**60**	**60**		**100.0 %**	**2.18 [0.80, 5.90]**
Total events: 12 (cont E+P), 6 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
6 Low dose E + 25g gestodene (continuous)					
Byrjalsen 1999	14/55	2/56		100.0 %	5.80 [2.02, 16.65]

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Study or subgroup	cont E+P n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**55**	**56**		**100.0 %**	**5.80 [2.02, 16.65]**
Total events: 14 (cont E+P), 2 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.27 (P = 0.0011)					
7 Moderate dose E + 0.5 mg NETA (continuous)					
Portman 2003	24/119	9/117		100.0 %	2.81 [1.35, 5.85]
Subtotal (95% CI)	**119**	**117**		**100.0 %**	**2.81 [1.35, 5.85]**
Total events: 24 (cont E+P), 9 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.76 (P = 0.0058)					
8 Moderate dose E + 1 mg NETA (continuous)					
Byrjalsen 2000	11/50	3/50		20.1 %	3.73 [1.21, 11.47]
Greenwald 2005	8/48	11/48		25.4 %	0.68 [0.25, 1.84]
Obel 1993	8/50	1/51		13.7 %	5.54 [1.42, 21.65]
Portman 2003	19/120	9/117		40.9 %	2.18 [0.99, 4.78]
Subtotal (95% CI)	**268**	**266**		**100.0 %**	**2.05 [1.24, 3.39]**
Total events: 46 (cont E+P), 24 (placebo)					
Heterogeneity: Chi^2 = 7.88, df = 3 (P = 0.05); I^2 =62%					
Test for overall effect: Z = 2.79 (P = 0.0053)					
Test for subgroup differences: Chi^2 = 13.21, df = 7 (P = 0.07), I^2 =47%					

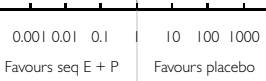
Analysis 3.1. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 1 Endometrial hyperplasia at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 1 Endometrial hyperplasia at 1 year

Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose E (day 1-28) + 10mg MPA (day 1-12)				
PEPI 1995	1/118	0/119		7.45 [0.15, 375.57]
Subtotal (95% CI)	**118**	**119**		**7.45 [0.15, 375.57]**
Total events: 1 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
2 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)				
PEPI 1995	2/120	0/119		7.39 [0.46, 118.84]
Subtotal (95% CI)	**120**	**119**		**7.39 [0.46, 118.84]**
Total events: 2 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.41 (P = 0.16)				
3 High dose E (day 1-21) + 10mg MPA (day 12-21)				
Heikkinen 1997	2/24	1/25		2.09 [0.21, 21.13]
Subtotal (95% CI)	**24**	**25**		**2.09 [0.21, 21.13]**
Total events: 2 (seq E + P), 1 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.63 (P = 0.53)				
4 High dose E (day 1-84) + 10 mg MPA (day 71-84) - longcycle				
Heikkinen 1997	0/26	0/26		0.0 [0.0, 0.0]
Subtotal (95% CI)	**26**	**26**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.59, df = 2 (P = 0.75), I^2 =0.0%				



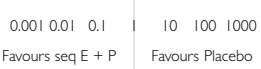
Analysis 3.2. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 2 Cumulative endometrial hyperplasia at 2 years

Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 5 mg dydrogesterone (days 15-28)				
Ferenczy 2002	0/100	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**100**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low dose E + 10 mg dydrogesterone (days 15-28)				
Ferenczy 2002	0/95	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**95**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Low dose E + 25g gestodene (day 17-28)				
Byrjalsen 1999	0/34	0/43		0.0 [0.0, 0.0]
Subtotal (95% CI)	**34**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Low dose E + 0.35mg NETA (days 4-6, 10-12, 16-18 ....)				
Byrjalsen 2000	0/32	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**32**	**25**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
5 Moderate dose E + 150g desogestrel (days 13-24)				
Byrjalsen 1992	0/20	0/18		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**18**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
6 Moderate dose E (day 1-22) + 1mg NETA (day 13-22) + low dose E (day 23-28)				
Obel 1993	0/45	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**



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Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
7 Moderate dose E (day 1-28) + 10mg MPA (day 1-12)				
PEPI 1995	4/118	0/119		7.65 [1.06, 54.98]
Subtotal (95% CI)	**118**	**119**		**7.65 [1.06, 54.98]**
Total events: 4 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.02 (P = 0.043)				
8 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)				
PEPI 1995	3/120	0/119		7.45 [0.77, 72.33]
Subtotal (95% CI)	**120**	**119**		**7.45 [0.77, 72.33]**
Total events: 3 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.73 (P = 0.083)				
9 Moderate dose E + 10 mg dydrogesterone (days 15-28)				
Ferenczy 2002	0/88	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**88**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
10 Moderate dose E + 20 mg dydrogesterone (days 15-28)				
Ferenczy 2002	0/96	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**96**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
11 Moderate dose E + 0.7mg NETA (days 4-6, 10-12, 16-18 ....)				
Byrjalsen 2000	0/26	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**26**	**25**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
12 Moderate dose E + 25g gestodene (day 17-28)				
Byrjalsen 1999	0/27	0/43		0.0 [0.0, 0.0]
Subtotal (95% CI)	**27**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
13 Moderate dose E + 50 g gestodene (day 17-28)				
Byrjalsen 1999	0/30	0/43		0.0 [0.0, 0.0]

0.001 0.01 0.1 1 10 100 1000

Favours seq E + P Favours Placebo

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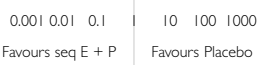
Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**30**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
14 High dose E (day 1-21) + 10mg MPA (day 12-21)				
Byrjalsen 1992	0/18	0/18		0.0 [0.0, 0.0]
Heikkinen 1997	3/23	1/25		3.19 [0.42, 24.21]
Subtotal (95% CI)	**41**	**43**		**3.19 [0.42, 24.21]**
Total events: 3 (seq E + P), 1 (Placebo)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.12 (P = 0.26)				
15 High dose E (day 1-84) + 10 mg MPA (day 71-84) - longcycle				
Heikkinen 1997	0/21	1/25		0.16 [0.00, 8.12]
Subtotal (95% CI)	**21**	**25**		**0.16 [0.00, 8.12]**
Total events: 0 (seq E + P), 1 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.92 (P = 0.36)				
Test for subgroup differences: Chi^2 = 3.33, df = 3 (P = 0.34), I^2 =10%				



Analysis 3.3. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 3 Cumulative endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 3 Cumulative endometrial hyperplasia at 3 years

Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E (day 1-182) + 100 mg progesterone (day 168-182)					
Prestwood 2003	1/51	1/57		100.0 %	1.12 [0.07, 18.20]
Subtotal (95% CI)	**51**	**57**		**100.0 %**	**1.12 [0.07, 18.20]**
Total events: 1 (seq E + P), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					
2 Moderate dose E (day 1-28) + 10 mg MPA (day 1-12)					
PEPI 1995	6/118	2/119		100.0 %	2.83 [0.69, 11.54]
Subtotal (95% CI)	**118**	**119**		**100.0 %**	**2.83 [0.69, 11.54]**
Total events: 6 (seq E + P), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
3 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)					
PEPI 1995	6/120	2/119		100.0 %	2.78 [0.68, 11.34]
Subtotal (95% CI)	**120**	**119**		**100.0 %**	**2.78 [0.68, 11.34]**
Total events: 6 (seq E + P), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.15)					
Test for subgroup differences: Chi^2 = 0.37, df = 2 (P = 0.83), I^2 =0.0%					

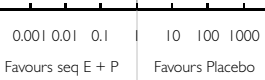
Analysis 3.4. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 4 Cumulative endometrial cancer at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 4 Cumulative endometrial cancer at 2 years

Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 5 mg dydrogesterone (days 15-28)				
Ferenczy 2002	1/100	0/63		5.10 [0.09, 285.72]
Subtotal (95% CI)	**100**	**63**		**5.10 [0.09, 285.72]**
Total events: 1 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.79 (P = 0.43)				
2 Low dose E + 10 mg dydrogesterone (days 15-28)				
Ferenczy 2002	0/95	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**95**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Low dose E + 25g gestodene (day 17-28)				
Byrjalsen 1999	0/34	0/43		0.0 [0.0, 0.0]
Subtotal (95% CI)	**34**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Moderate dose E + 10 mg dydrogesterone (days 15-28)				
Ferenczy 2002	0/88	0/63		0.0 [0.0, 0.0]
Subtotal (95% CI)	**88**	**63**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
5 Moderate dose E + 20 mg dydrogesterone (days 15-28)				
Ferenczy 2002	2/96	0/63		5.30 [0.31, 90.86]
Subtotal (95% CI)	**96**	**63**		**5.30 [0.31, 90.86]**
Total events: 2 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.15 (P = 0.25)				
6 Moderate dose E + 1 mg NETA (sequential)				
Obel 1993	0/45	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**



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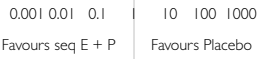
Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
7 Moderate dose E + 25g gestodene (day 17-28)				
Byrjalsen 1999	0/27	0/43		0.0 [0.0, 0.0]
Subtotal (95% CI)	**27**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
8 Moderate dose E + 50 g gestodene (day 17-28)				
Byrjalsen 1999	0/30	0/43		0.0 [0.0, 0.0]
Subtotal (95% CI)	**30**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
9 Moderate dose E (day 1-22) + 1mg NETA (day 13-22) + low dose E (day 23-28)				
Obel 1993	0/45	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**45**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (seq E + P), 0 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.99), I^2 =0.0%				



Analysis 3.5. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 5 Cumulative endometrial cancer at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 5 Cumulative endometrial cancer at 3 years

Study or subgroup	E + P (seq) n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E (day 1-28) +10 mg MPA (day 1-12)					
PEPI 1995	0/118	1/119		100.0 %	0.33 [0.01, 8.27]
Subtotal (95% CI)	**118**	**119**		**100.0 %**	**0.33 [0.01, 8.27]**
Total events: 0 (E + P (seq)), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
2 Moderate dose E (day 1-28) + 200mg progesterone(days 1-12)					
PEPI 1995	0/120	1/119		100.0 %	0.33 [0.01, 8.13]
Subtotal (95% CI)	**120**	**119**		**100.0 %**	**0.33 [0.01, 8.13]**
Total events: 0 (E + P (seq)), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					

Analysis 3.6. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 6 Additional investigations (unscheduled biopsy).

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 6 Additional investigations (unscheduled biopsy)

Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E (day 1-182) + 100 mg progesterone (day 168-182)					
Prestwood 2003	3/51	1/57		100.0 %	3.15 [0.43, 23.05]
Subtotal (95% CI)	**51**	**57**		**100.0 %**	**3.15 [0.43, 23.05]**
Total events: 3 (seq E + P), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					
2 Moderate dose E (day 1-28) +10 mg MPA (day 1-12)					
PEPI 1995	16/118	10/119		100.0 %	1.69 [0.75, 3.81]
Subtotal (95% CI)	**118**	**119**		**100.0 %**	**1.69 [0.75, 3.81]**
Total events: 16 (seq E + P), 10 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.21)					
3 Moderate dose E (day 1-28) +200mg progesterone (day 1-12)					
PEPI 1995	14/120	10/119		100.0 %	1.43 [0.62, 3.33]
Subtotal (95% CI)	**120**	**119**		**100.0 %**	**1.43 [0.62, 3.33]**
Total events: 14 (seq E + P), 10 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
Test for subgroup differences: Chi^2 = 0.52, df = 2 (P = 0.77), I^2 =0.0%					

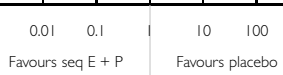
Analysis 3.7. Comparison 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO, Outcome 7 Withdrawal due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 3 ESTROGEN + PROGESTOGEN (sequential) VS PLACEBO

Outcome: 7 Withdrawal due to adverse events

Study or subgroup	seq E + P n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 5 mg dydrogesterone (days 15-28)					
Ferenczy 2002	17/117	12/113		100.0 %	1.42 [0.65, 3.10]
Subtotal (95% CI)	**117**	**113**		**100.0 %**	**1.42 [0.65, 3.10]**
Total events: 17 (seq E + P), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.37)					
2 Low dose E + 10 mg dydrogesterone (days 15-28)					
Ferenczy 2002	17/114	12/113		100.0 %	1.47 [0.67, 3.19]
Subtotal (95% CI)	**114**	**113**		**100.0 %**	**1.47 [0.67, 3.19]**
Total events: 17 (seq E + P), 12 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					
3 Low dose E + 25g gestodene (day 17-28)					
Byrjalsen 1999	17/56	2/56		100.0 %	6.58 [2.46, 17.58]
Subtotal (95% CI)	**56**	**56**		**100.0 %**	**6.58 [2.46, 17.58]**
Total events: 17 (seq E + P), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.76 (P = 0.00017)					
4 Low dose E + 0.35mg NETA (days 4-6, 10-12, 16-18 ....)					
Byrjalsen 2000	7/50	3/50		100.0 %	2.41 [0.66, 8.85]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**2.41 [0.66, 8.85]**
Total events: 7 (seq E + P), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					
5 Moderate dose E + 50 g desogestrel (days 12-21)					
Byrjalsen 1992	5/25	5/23		100.0 %	0.90 [0.23, 3.58]
Subtotal (95% CI)	**25**	**23**		**100.0 %**	**0.90 [0.23, 3.58]**
Total events: 5 (seq E + P), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.15 (P = 0.88)					
6 Moderate dose E + 10 mg dydrogesterone (days 15-28)					
Ferenczy 2002	17/117	12/113		100.0 %	1.42 [0.65, 3.10]
Subtotal (95% CI)	**117**	**113**		**100.0 %**	**1.42 [0.65, 3.10]**



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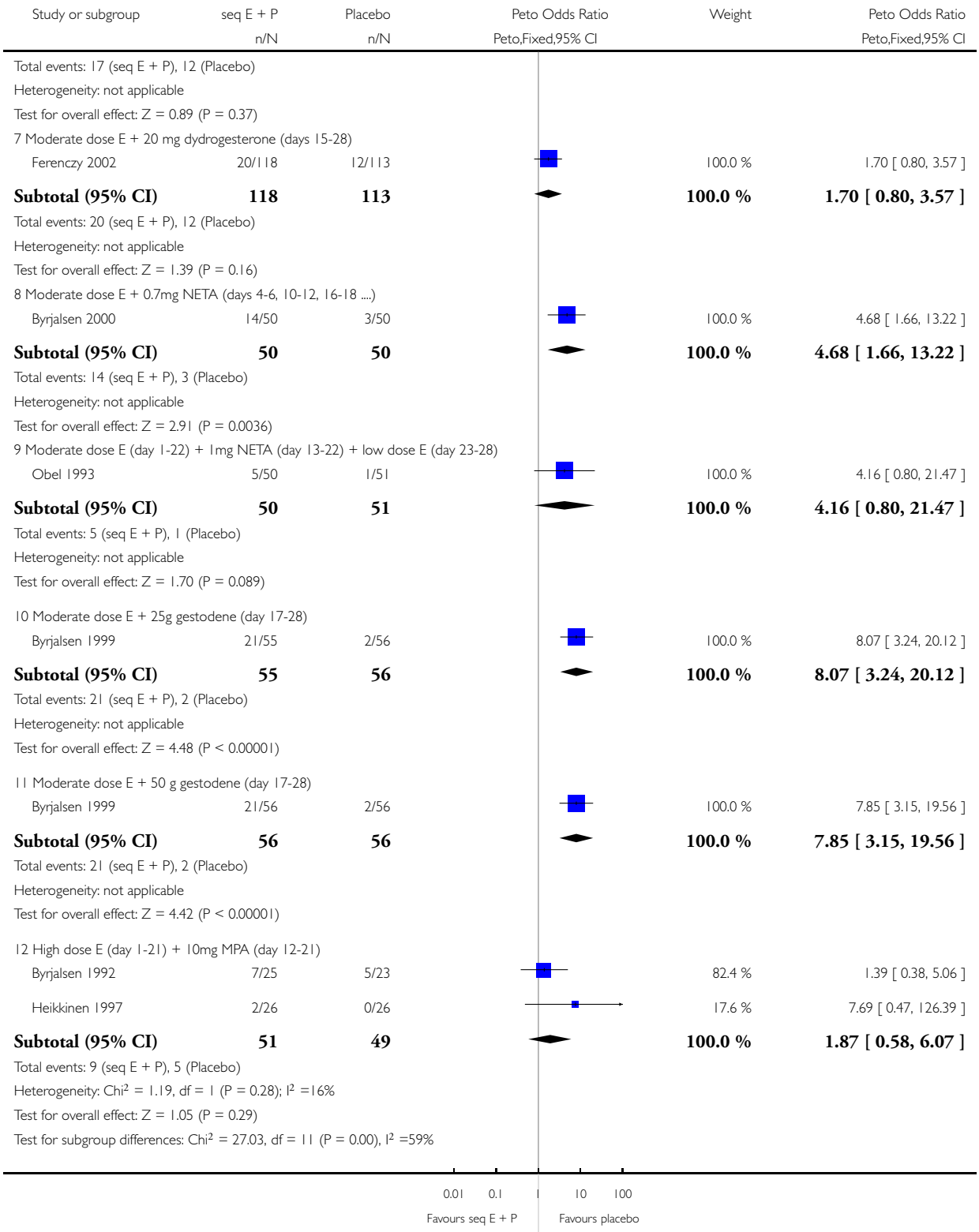


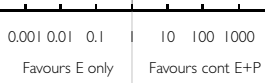
Analysis 4.1. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 1 Endometrial hyperplasia at one year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 1 Endometrial hyperplasia at one year

Study or subgroup	E only n/N	Cont E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed low dose E vs low dose E + 0.5 mg drospirinone					
Archer 2005	8/226	0/227		100.0 %	7.66 [1.89, 30.96]
Subtotal (95% CI)	**226**	**227**		**100.0 %**	**7.66 [1.89, 30.96]**
Total events: 8 (E only), 0 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.86 (P = 0.0043)					
2 Unopposed low dose E vs low dose E + 1 mg drospirinone					
Archer 2005	8/226	0/231		100.0 %	7.80 [1.93, 31.51]
Subtotal (95% CI)	**226**	**231**		**100.0 %**	**7.80 [1.93, 31.51]**
Total events: 8 (E only), 0 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.88 (P = 0.0040)					
3 Unopposed low dose E vs low dose E + 2 mg drospirinone					
Archer 2005	8/226	1/227		100.0 %	4.89 [1.31, 18.29]
Subtotal (95% CI)	**226**	**227**		**100.0 %**	**4.89 [1.31, 18.29]**
Total events: 8 (E only), 1 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
4 Unopposed low dose E vs low dose E + 3 mg drospirinone					
Archer 2005	8/226	0/231		100.0 %	7.80 [1.93, 31.51]
Subtotal (95% CI)	**226**	**231**		**100.0 %**	**7.80 [1.93, 31.51]**
Total events: 8 (E only), 0 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.88 (P = 0.0040)					
5 Unopposed low dose E vs low dose E + 1.5 mg MPA					
HOPE 2001	10/548	2/544		100.0 %	3.82 [1.22, 11.90]
Subtotal (95% CI)	**548**	**544**		**100.0 %**	**3.82 [1.22, 11.90]**
Total events: 10 (E only), 2 (Cont E + P)					
Heterogeneity: not applicable					



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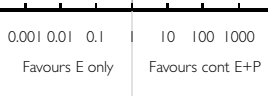
Study or subgroup	E only n/N	Cont E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: Z = 2.31 (P = 0.021)					
6 Unopposed low dose E vs low dose E + 2.5 mg MPA					
HOPE 2001	10/548	0/273		100.0 %	4.55 [1.21, 17.08]
Subtotal (95% CI)	**548**	**273**		**100.0 %**	**4.55 [1.21, 17.08]**
Total events: 10 (E only), 0 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.24 (P = 0.025)					
7 Unopposed low dose E vs low dose E + 0.1 mg NETA					
Kurman 2000	36/247	2/249		100.0 %	6.98 [3.60, 13.52]
Subtotal (95% CI)	**247**	**249**		**100.0 %**	**6.98 [3.60, 13.52]**
Total events: 36 (E only), 2 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.76 (P < 0.00001)					
8 Unopposed low dose E vs low dose E + 0.2/0.25mg NETA					
CHART 1996	1/259	0/80		1.9 %	3.70 [0.04, 374.18]
Kurman 2000	36/247	1/251		92.7 %	7.82 [4.01, 15.28]
Portman 2003	1/114	1/114		5.4 %	1.00 [0.06, 16.09]
Subtotal (95% CI)	**620**	**445**		**100.0 %**	**6.90 [3.62, 13.15]**
Total events: 38 (E only), 2 (Cont E + P)					
Heterogeneity: Chi^2 = 2.06, df = 2 (P = 0.36); I^2 =3%					
Test for overall effect: Z = 5.88 (P < 0.00001)					
9 Unopposed low dose E vs low dose E + 0.5 mg NETA					
CHART 1996	1/259	0/69		1.9 %	3.55 [0.03, 434.99]
Kurman 2000	36/247	1/241		98.1 %	7.51 [3.85, 14.68]
Subtotal (95% CI)	**506**	**310**		**100.0 %**	**7.41 [3.82, 14.38]**
Total events: 37 (E only), 1 (Cont E + P)					
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 5.92 (P < 0.00001)					
10 Unopposed low dose E vs low dose E + 1 mg NETA					
CHART 1996	1/259	0/65		39.1 %	3.49 [0.03, 466.48]
Portman 2003	1/114	0/121		60.9 %	7.86 [0.16, 396.66]
Subtotal (95% CI)	**373**	**186**		**100.0 %**	**5.72 [0.27, 122.11]**
Total events: 2 (E only), 0 (Cont E + P)					
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 1.12 (P = 0.26)					
11 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA					
HOPE 2001	20/249	0/278		20.3 %	8.99 [3.68, 21.98]
MSG 1994	57/283	2/279		55.9 %	7.87 [4.59, 13.50]
PEPI 1995	25/119	0/120		23.8 %	9.33 [4.08, 21.34]



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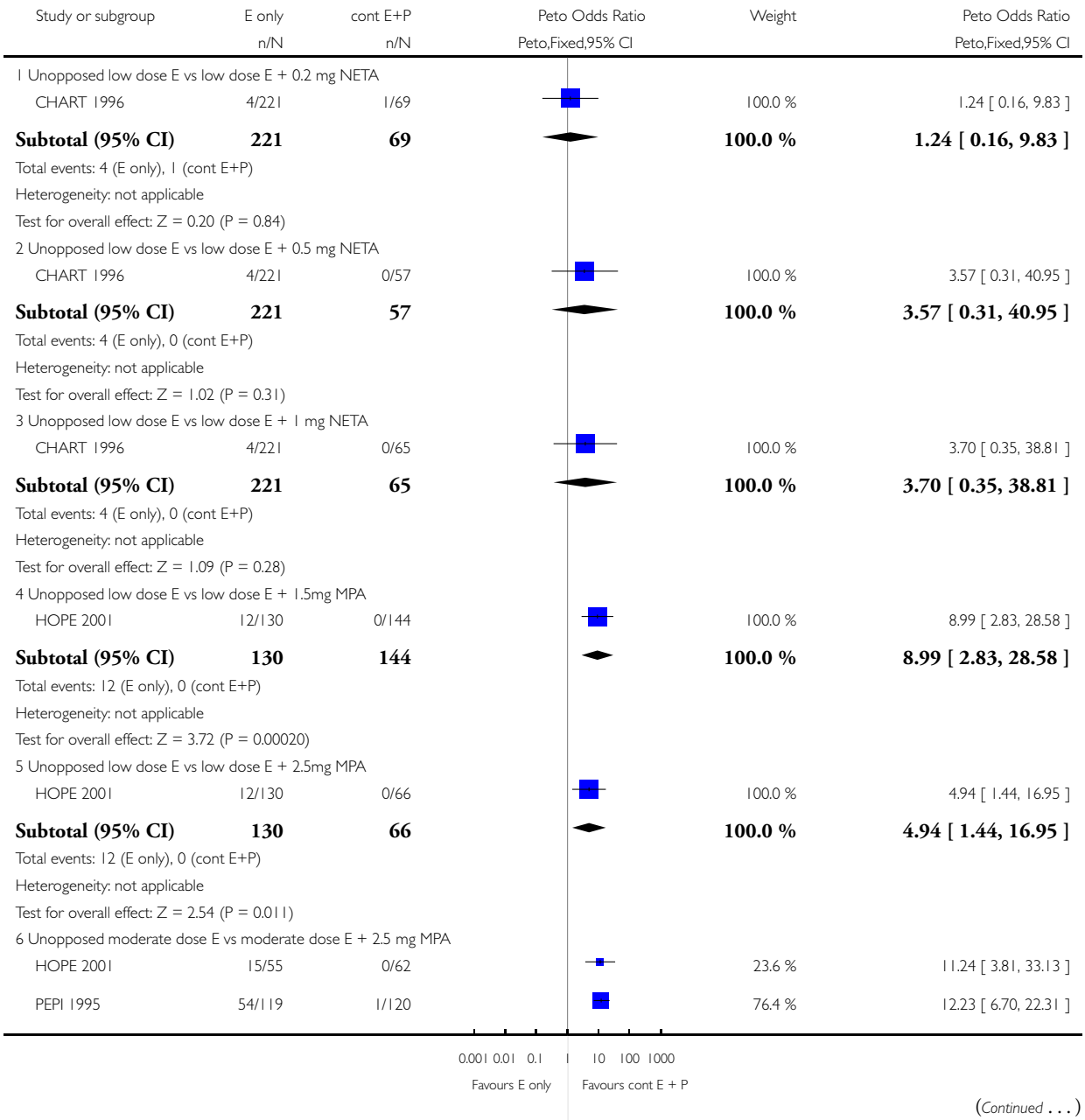
Study or subgroup	E only n/N	Cont E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**651**	**677**		**100.0 %**	**8.42 [5.63, 12.60]**
Total events: 102 (E only), 2 (Cont E + P)					
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² =0.0%					
Test for overall effect: Z = 10.36 (P < 0.00001)					
12 Unopposed moderate dose E vs moderate dose E + 5 mg MPA					
MSG 1994	57/283	0/274		100.0 %	8.92 [5.16, 15.43]
Subtotal (95% CI)	**283**	**274**		**100.0 %**	**8.92 [5.16, 15.43]**
Total events: 57 (E only), 0 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.83 (P < 0.00001)					
13 Unopposed moderate dose E vs moderate dose E + 0.5 mg NETA					
Prestwood 2003	23/118	0/115		100.0 %	8.86 [3.75, 20.92]
Subtotal (95% CI)	**118**	**115**		**100.0 %**	**8.86 [3.75, 20.92]**
Total events: 23 (E only), 0 (Cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.98 (P < 0.00001)					
14 Unopposed moderate dose E vs moderate dose E + 1 mg NETA					
CHART 1996	9/61	0/71		28.7 %	10.02 [2.59, 38.75]
Prestwood 2003	23/118	0/119		71.3 %	9.16 [3.88, 21.61]
Subtotal (95% CI)	**179**	**190**		**100.0 %**	**9.40 [4.55, 19.40]**
Total events: 32 (E only), 0 (Cont E + P)					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² =0.0%					
Test for overall effect: Z = 6.06 (P < 0.00001)					
Test for subgroup differences: Chi² = 3.63, df = 13 (P = 0.99), I² =0.0%					

Analysis 4.2. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 2 Cumulative endometrial hyperplasia at 2 years



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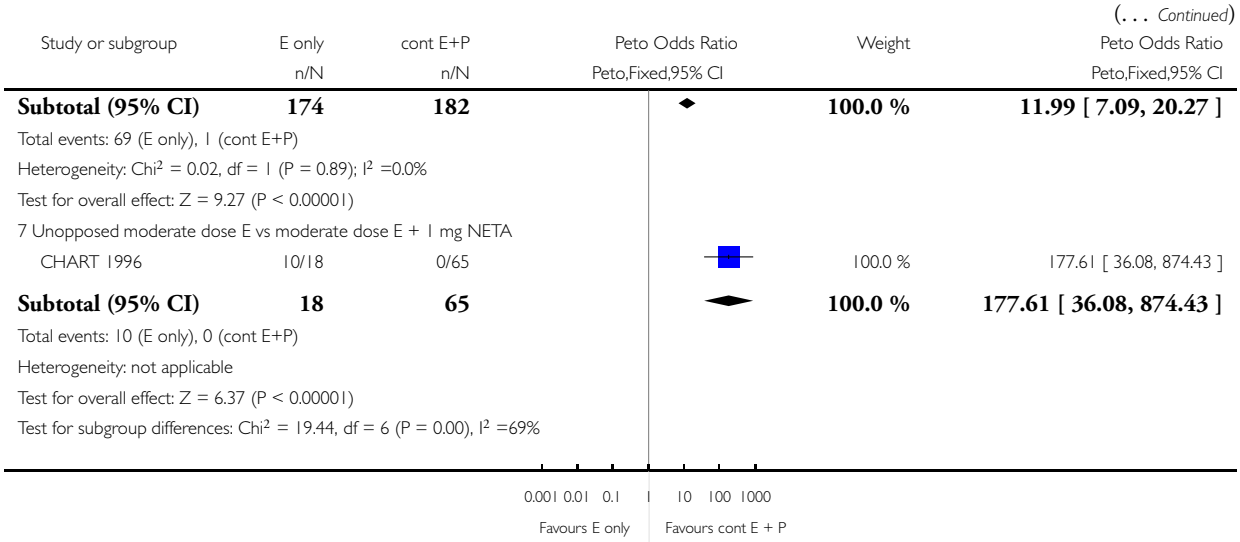
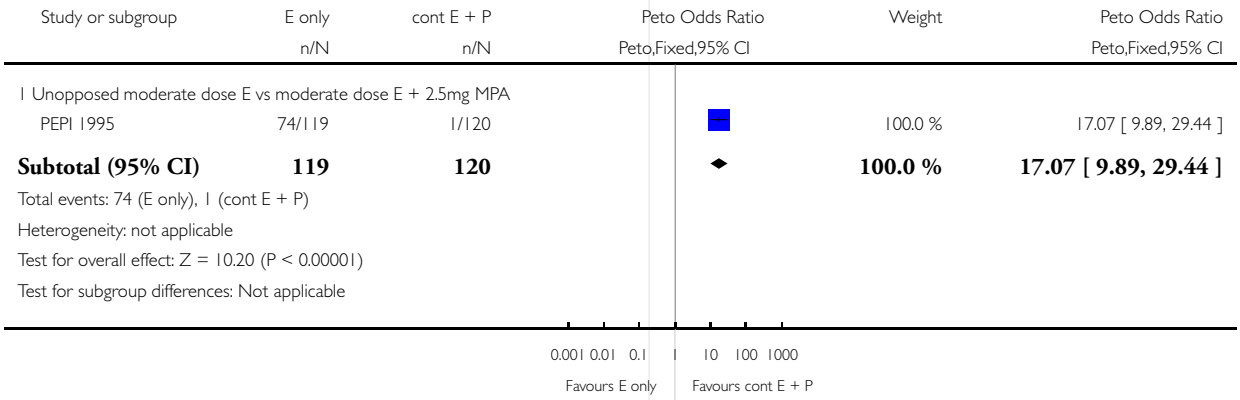


Analysis 4.3. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 3 Cumulative endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 3 Cumulative endometrial hyperplasia at 3 years



Analysis 4.4. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 4 Endometrial cancer at one year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 4 Endometrial cancer at one year

Study or subgroup	E only n/N	cont E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed low dose E vs low dose E + 0.1 mg NETA				
Kurman 2000	0/247	0/249		0.0 [0.0, 0.0]
Subtotal (95% CI)	**247**	**249**		**0.0 [0.0, 0.0]**
Total events: 0 (E only), 0 (cont E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Unopposed low dose E vs low dose E + 0.2/0.25 mg NETA				
Kurman 2000	0/247	0/251		0.0 [0.0, 0.0]
Subtotal (95% CI)	**247**	**251**		**0.0 [0.0, 0.0]**
Total events: 0 (E only), 0 (cont E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Unopposed low dose E vs low dose E + 0.5 mg NETA				
Kurman 2000	0/247	0/241		0.0 [0.0, 0.0]
Subtotal (95% CI)	**247**	**241**		**0.0 [0.0, 0.0]**
Total events: 0 (E only), 0 (cont E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Unopposed moderate dose E vs moderate dose E + 2.5 MPA				
MSG 1994	1/283	0/279		7.29 [0.14, 367.19]
Subtotal (95% CI)	**283**	**279**		**7.29 [0.14, 367.19]**
Total events: 1 (E only), 0 (cont E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.99 (P = 0.32)				
5 Unopposed moderate dose E vs moderate dose E + 5 MPA				
MSG 1994	1/283	0/274		7.16 [0.14, 360.91]
Subtotal (95% CI)	**283**	**274**		**7.16 [0.14, 360.91]**
Total events: 1 (E only), 0 (cont E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.98 (P = 0.33)				
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 1.00), I^2 =0.0%				

Analysis 4.5. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 5 Endometrial cancer at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 5 Endometrial cancer at 3 years

Study or subgroup	E only n/N	cont E+P n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E +2.5mg MPA				
PEPI 1995	0/119	0/120		0.0 [0.0, 0.0]
Total (95% CI)	**119**	**120**		**0.0 [0.0, 0.0]**

Total events: 0 (E only), 0 (cont E+P)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%

Analysis 4.6. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 6 Adherence to therapy.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 6 Adherence to therapy

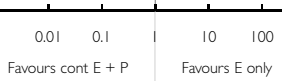
Study or subgroup	E only n/N	cont E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA					
PEPI 1995	52/119	102/120		100.0 %	0.17 [0.10, 0.28]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**0.17 [0.10, 0.28]**

Total events: 52 (E only), 102 (cont E + P)

Heterogeneity: not applicable

Test for overall effect: Z = 6.66 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 4.7. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 7 Additional investigations (unscheduled biopsy).

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 7 Additional investigations (unscheduled biopsy)

Study or subgroup	E only n/N	cont E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E + 2.5 MPA					
PEPI 1995	79/119	9/120		100.0 %	12.44 [7.36, 21.02]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**12.44 [7.36, 21.02]**
Total events: 79 (E only), 9 (cont E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.42 (P < 0.00001)					
Test for subgroup differences: Not applicable					

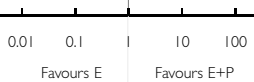
Analysis 4.8. Comparison 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous), Outcome 8 Withdrawal due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 4 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (continuous)

Outcome: 8 Withdrawal due to adverse events

Study or subgroup	E only n/N	cont E+P n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Unopposed low dose E vs low dose E + 1.5 mg MPA (cont)					
HOPE 2001	17/212	10/210		11.7 %	1.74 [0.78, 3.90]
Subtotal (95% CI)	**212**	**210**		**11.7 %**	**1.74 [0.78, 3.90]**
Total events: 17 (E only), 10 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.35 (P = 0.18)					
2 Unopposed low dose E vs low dose E + 2.5 mg MPA (cont)					
HOPE 2001	17/212	5/108		7.7 %	1.80 [0.64, 5.01]
Subtotal (95% CI)	**212**	**108**		**7.7 %**	**1.80 [0.64, 5.01]**
Total events: 17 (E only), 5 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
3 Unopposed low dose E vs low dose E +0.25 mg NETA					
Portman 2003	10/115	11/115		12.7 %	0.90 [0.37, 2.21]
Subtotal (95% CI)	**115**	**115**		**12.7 %**	**0.90 [0.37, 2.21]**
Total events: 10 (E only), 11 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
4 Unopposed low dose E vs low dose E + 1 mg NETA					
Portman 2003	10/115	13/121		14.6 %	0.79 [0.33, 1.88]
Subtotal (95% CI)	**115**	**121**		**14.6 %**	**0.79 [0.33, 1.88]**
Total events: 10 (E only), 13 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
5 Unopposed moderate dose E vs moderate dose E + 2.5 mg MPA (cont)					
HOPE 2001	22/103	6/121		5.5 %	5.21 [2.02, 13.41]
Subtotal (95% CI)	**103**	**121**		**5.5 %**	**5.21 [2.02, 13.41]**
Total events: 22 (E only), 6 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.42 (P = 0.00063)					
6 Unopposed moderate dose E vs moderate dose E + 0.5 mg NETA					
Prestwood 2003	14/119	24/119		26.8 %	0.53 [0.26, 1.08]
Subtotal (95% CI)	**119**	**119**		**26.8 %**	**0.53 [0.26, 1.08]**



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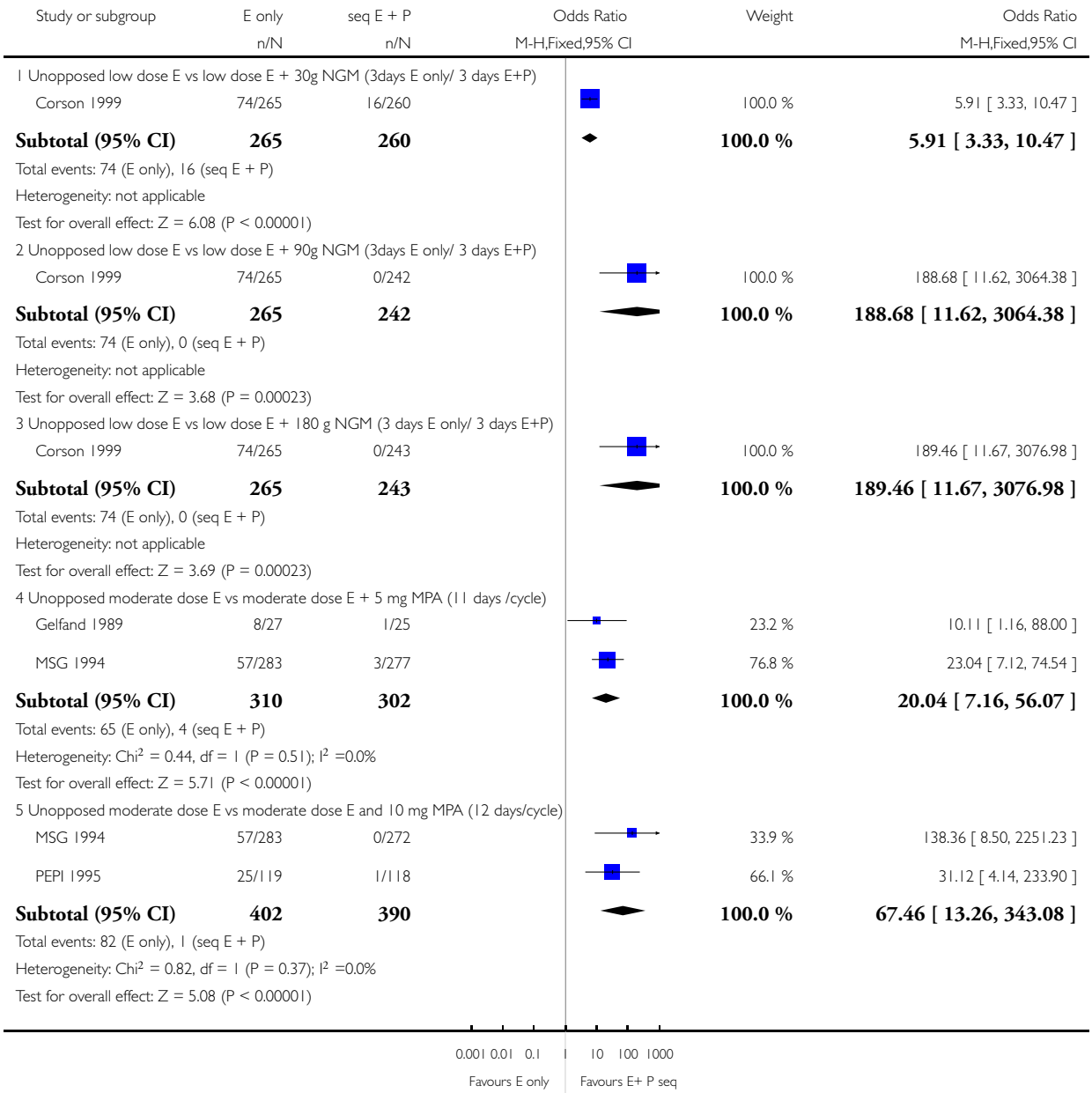
Study or subgroup	E only n/N	cont E+P n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 14 (E only), 24 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.080)					
7 Unopposed moderate dose E vs moderate dose E + 1 mg NETA					
Prestwood 2003	14/119	19/120		21.1 %	0.71 [0.34, 1.49]
Subtotal (95% CI)	**119**	**120**		**21.1 %**	**0.71 [0.34, 1.49]**
Total events: 14 (E only), 19 (cont E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					
Total (95% CI)	**995**	**914**		**100.0 %**	**1.15 [0.85, 1.55]**
Total events: 104 (E only), 88 (cont E+P)					
Heterogeneity: Chi^2 = 18.71, df = 6 (P = 0.005); I^2 =68%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Test for subgroup differences: Chi^2 = 0.0, df = 6 (P = 0.0), I^2 =0.0%					

Analysis 5.1. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 1 Endometrial hyperplasia at one year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 1 Endometrial hyperplasia at one year



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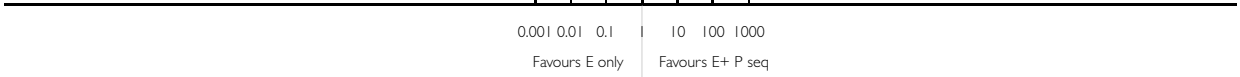
Study or subgroup	E only n/N	seq E + P n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
6 Unopposed moderate dose E vs moderate dose E + 10 mg progesterone (12days/cycle)					
PEPI 1995	25/119	2/120		100.0 %	15.69 [3.62, 67.94]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**15.69 [3.62, 67.94]**
Total events: 25 (E only), 2 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.68 (P = 0.00023)					
7 Unopposed high dose E vs high dose E + 5 mg MPA (11days/cycle)					
Gelfand 1989	13/23	2/20		100.0 %	11.70 [2.19, 62.62]
Subtotal (95% CI)	**23**	**20**		**100.0 %**	**11.70 [2.19, 62.62]**
Total events: 13 (E only), 2 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.87 (P = 0.0041)					



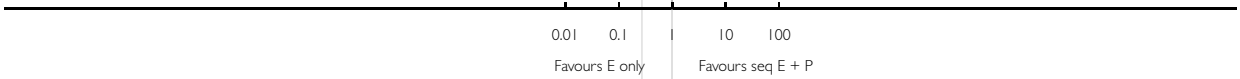
Analysis 5.2. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 2 Cumulative endometrial hyperplasia at 2 years

Study or subgroup	E only n/N	seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E + 10 mg MPA (sequential)					
PEPI 1995	54/119	4/118		100.0 %	9.60 [5.32, 17.34]
Subtotal (95% CI)	**119**	**118**		**100.0 %**	**9.60 [5.32, 17.34]**
Total events: 54 (E only), 4 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.50 (P < 0.00001)					
2 Unopposed moderate dose E vs moderate dose E and 10 mg progesterone (sequential)					
PEPI 1995	54/119	3/120		100.0 %	10.50 [5.80, 19.01]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**10.50 [5.80, 19.01]**
Total events: 54 (E only), 3 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.76 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 =0.0%					



Analysis 5.3. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 3 Cumulative endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 3 Cumulative endometrial hyperplasia at 3 years

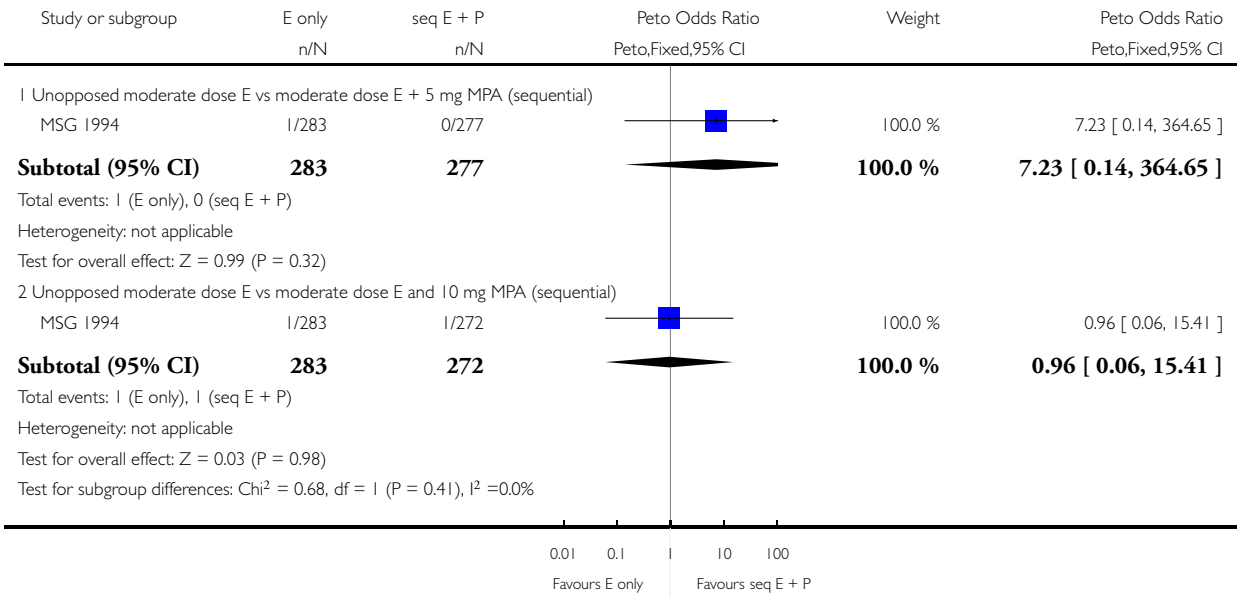
Study or subgroup	E only n/N	seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E + 10 mg MPA (sequential)					
PEPI 1995	74/119	6/118		100.0 %	12.71 [7.43, 21.76]
Subtotal (95% CI)	**119**	**118**		**100.0 %**	**12.71 [7.43, 21.76]**
Total events: 74 (E only), 6 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.27 (P < 0.00001)					
2 Unopposed moderate dose vs moderate dose E and 10 mg progesterone (sequential)					
PEPI 1995	74/119	6/120		100.0 %	12.90 [7.55, 22.05]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**12.90 [7.55, 22.05]**
Total events: 74 (E only), 6 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.35 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.97), I^2 =0.0%					

Analysis 5.4. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 4 Endometrial cancer at one year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 4 Endometrial cancer at one year



Analysis 5.5. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 5 Endometrial cancer at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 5 Endometrial cancer at 3 years

Study or subgroup	E only n/N	seq E + P n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E and 10 mg MPA (sequential)				
PEPI 1995	0/119	0/118		0.0 [0.0, 0.0]
Subtotal (95% CI)	**119**	**118**		**0.0 [0.0, 0.0]**
Total events: 0 (E only), 0 (seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Unopposed moderate dose E vs moderate dose E + 10 mg progesterone (sequential)				
PEPI 1995	0/119	0/120		0.0 [0.0, 0.0]
Subtotal (95% CI)	**119**	**120**		**0.0 [0.0, 0.0]**
Total events: 0 (E only), 0 (seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**238**	**238**		**0.0 [0.0, 0.0]**
Total events: 0 (E only), 0 (seq E + P)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

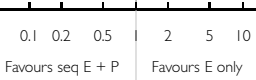
Analysis 5.6. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 6 Adherence to therapy.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 6 Adherence to therapy

Study or subgroup	E only n/N	seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E and 10 mg MPA (sequential)					
PEPI 1995	52/119	96/118		100.0 %	0.20 [0.12, 0.34]
Subtotal (95% CI)	**119**	**118**		**100.0 %**	**0.20 [0.12, 0.34]**
Total events: 52 (E only), 96 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.97 (P < 0.00001)					
2 Unopposed moderate dose E vs moderate dose E + 10 mg progesterone (sequential)					
PEPI 1995	52/119	96/120		100.0 %	0.22 [0.13, 0.36]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**0.22 [0.13, 0.36]**
Total events: 52 (E only), 96 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.77 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.86), I^2 =0.0%					



Analysis 5.7. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 7 Additional investigations (endometrial biopsy).

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 7 Additional investigations (endometrial biopsy)

Study or subgroup	E only n/N	seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed moderate dose E vs moderate dose E + 10 mg MPA (sequential)					
PEPI 1995	79/119	16/118		100.0 %	8.94 [5.32, 15.01]
Subtotal (95% CI)	**119**	**118**		**100.0 %**	**8.94 [5.32, 15.01]**
Total events: 79 (E only), 16 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 8.28 (P < 0.00001)					
2 Unopposed moderate dose E vs moderate dose E and 10 mg progesterone (sequential)					
PEPI 1995	79/119	14/120		100.0 %	9.90 [5.89, 16.63]
Subtotal (95% CI)	**119**	**120**		**100.0 %**	**9.90 [5.89, 16.63]**
Total events: 79 (E only), 14 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 8.66 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 =0.0%					

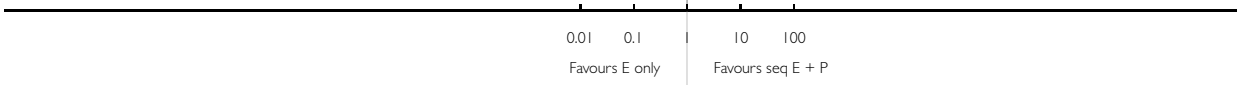
Analysis 5.8. Comparison 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential), Outcome 8 Withdrawal due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 5 UNOPPOSED ESTROGEN VS ESTROGEN/PROGESTOGEN (sequential)

Outcome: 8 Withdrawal due to adverse events

Study or subgroup	E only n/N	seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Unopposed low dose E vs low dose E + 30g NGM (3days E only/ 3 days E+P)					
Corson 1999	49/311	19/313		100.0 %	2.71 [1.64, 4.48]
Subtotal (95% CI)	**311**	**313**		**100.0 %**	**2.71 [1.64, 4.48]**
Total events: 49 (E only), 19 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.88 (P = 0.00010)					
2 Unopposed low dose E vs low dose E + 90g NGM (3days E only/ 3 days E+P)					
Corson 1999	49/311	23/313		100.0 %	2.28 [1.39, 3.72]
Subtotal (95% CI)	**311**	**313**		**100.0 %**	**2.28 [1.39, 3.72]**
Total events: 49 (E only), 23 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.28 (P = 0.0010)					
3 Unopposed low dose E vs low dose E + 180g NGM (3days E only/ 3 days E+P)					
Corson 1999	49/311	27/316		100.0 %	1.97 [1.22, 3.17]
Subtotal (95% CI)	**311**	**316**		**100.0 %**	**1.97 [1.22, 3.17]**
Total events: 49 (E only), 27 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.76 (P = 0.0057)					
4 Unopposed moderate dose E vs moderate dose E + 5 mg MPA (sequential)					
Gelfand 1989	4/42	6/41		100.0 %	0.62 [0.17, 2.31]
Subtotal (95% CI)	**42**	**41**		**100.0 %**	**0.62 [0.17, 2.31]**
Total events: 4 (E only), 6 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
5 Unopposed high dose E vs high dose E + 5 mg MPA (sequential)					
Gelfand 1989	4/44	13/46		100.0 %	0.29 [0.10, 0.83]
Subtotal (95% CI)	**44**	**46**		**100.0 %**	**0.29 [0.10, 0.83]**
Total events: 4 (E only), 13 (seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.31 (P = 0.021)					
Test for subgroup differences: Chi^2 = 17.53, df = 4 (P = 0.00), I^2 =77%					



Analysis 6.1. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 1 Endometrial hyperplasia at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 1 Endometrial hyperplasia at 1 year

Study or subgroup	Cont E + P n/N	Seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 14-25)				
Luciano 1993	0/10	0/8		0.0 [0.0, 0.0]
Subtotal (95% CI)	**10**	**8**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 15-28)				
MSG 1994	2/279	3/277		0.66 [0.11, 3.85]
Subtotal (95% CI)	**279**	**277**		**0.66 [0.11, 3.85]**
Total events: 2 (Cont E + P), 3 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.46 (P = 0.65)				
3 Moderate dose E + 5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 14-25)				
Luciano 1993	0/11	0/8		0.0 [0.0, 0.0]
Subtotal (95% CI)	**11**	**8**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Moderate dose E +5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 15-28)				
MSG 1994	0/274	0/272		0.0 [0.0, 0.0]
Subtotal (95% CI)	**274**	**272**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
5 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)				
PEPI 1995	0/120	1/118		0.13 [0.00, 6.71]
Subtotal (95% CI)	**120**	**118**		**0.13 [0.00, 6.71]**
Total events: 0 (Cont E + P), 1 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.01 (P = 0.31)				
6 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)				
PEPI 1995	0/120	2/120		0.13 [0.01, 2.16]
Subtotal (95% CI)	**120**	**120**		**0.13 [0.01, 2.16]**

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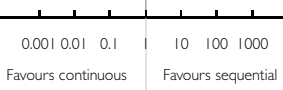
Study or subgroup	Cont E + P n/N	Seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 0 (Cont E + P), 2 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.42 (P = 0.16)				
7 Moderate dose E + 1 mg NETA (cont) vs low dose E + 90g NGM (days 4-6, 10-12 ....)				
Rozenberg 2001	0/185	0/176		0.0 [0.0, 0.0]
Subtotal (95% CI)	**185**	**176**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
8 Moderate dose E + 1 mg NETA (cont) vs low dose E + 180g NGM (days 4-6, 10-12 ....)				
Rozenberg 2001	0/185	0/110		0.0 [0.0, 0.0]
Subtotal (95% CI)	**185**	**110**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 1.20, df = 2 (P = 0.55), I^2 =0.0%				



Analysis 6.2. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 2 Cumulative endometrial hyperplasia at 2 years

Study or subgroup	Cont E + P n/N	Seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.35 mg NETA (day 4-6, 10-12 ...)				
Byrjalsen 2000	0/30	0/32		0.0 [0.0, 0.0]
Subtotal (95% CI)	**30**	**32**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.7 mg NETA (day 4-6, 10-12 ...)				
Byrjalsen 2000	0/30	0/26		0.0 [0.0, 0.0]
Subtotal (95% CI)	**30**	**26**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 1mg NETA (days 13-22)				
Obel 1993	0/39	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**39**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)				
PEPI 1995	1/120	4/118		0.29 [0.05, 1.70]
Subtotal (95% CI)	**120**	**118**		**0.29 [0.05, 1.70]**
Total events: 1 (Cont E + P), 4 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.37 (P = 0.17)				
5 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)				
PEPI 1995	1/120	3/120		0.36 [0.05, 2.61]
Subtotal (95% CI)	**120**	**120**		**0.36 [0.05, 2.61]**
Total events: 1 (Cont E + P), 3 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.01 (P = 0.31)				
6 Moderate dose E + 1 mg NETA (cont) vs low dose E + 90g NGM (days 4-6, 10-12 ....)				
Rozenberg 2001	0/157	0/125		0.0 [0.0, 0.0]
Subtotal (95% CI)	**157**	**125**		**0.0 [0.0, 0.0]**

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Study or subgroup	Cont E + P n/N	Seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 0 (Cont E + P), 0 (Seq E + P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² =0.0%				

Analysis 6.3. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 3 Cumulative endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 3 Cumulative endometrial hyperplasia at 3 years

Study or subgroup	Cont E + P n/N	Seq E + P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)					
PEPI 1995	1/120	6/118		100.0 %	0.23 [0.05, 1.02]
Subtotal (95% CI)	**120**	**118**		**100.0 %**	**0.23 [0.05, 1.02]**
Total events: 1 (Cont E + P), 6 (Seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.94 (P = 0.053)					
2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)					
PEPI 1995	1/120	6/120		100.0 %	0.23 [0.05, 1.04]
Subtotal (95% CI)	**120**	**120**		**100.0 %**	**0.23 [0.05, 1.04]**
Total events: 1 (Cont E + P), 6 (Seq E + P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.91 (P = 0.056)					
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² =0.0%					

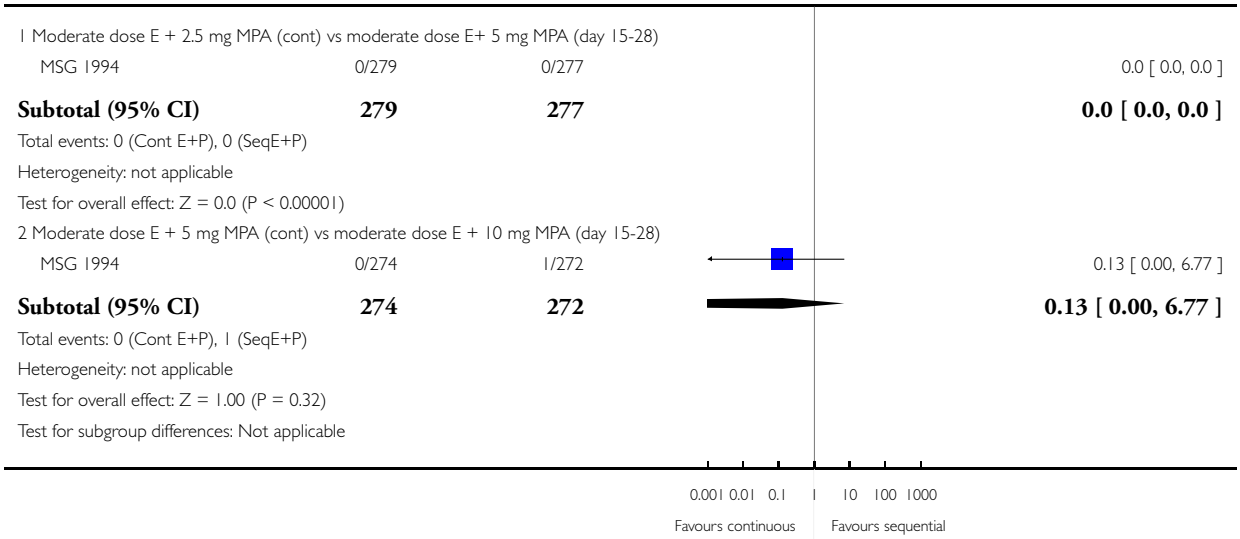
Analysis 6.4. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 4 Endometrial cancer at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 4 Endometrial cancer at 1 year

Study or subgroup	Cont E+P n/N	SeqE+P n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E+ 5 mg MPA (day 15-28)				
MSG 1994	0/279	0/277		0.0 [0.0, 0.0]
Subtotal (95% CI)	**279**	**277**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E+P), 0 (SeqE+P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose E + 5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 15-28)				
MSG 1994	0/274	1/272		0.13 [0.00, 6.77]
Subtotal (95% CI)	**274**	**272**		**0.13 [0.00, 6.77]**
Total events: 0 (Cont E+P), 1 (SeqE+P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
Test for subgroup differences: Not applicable				

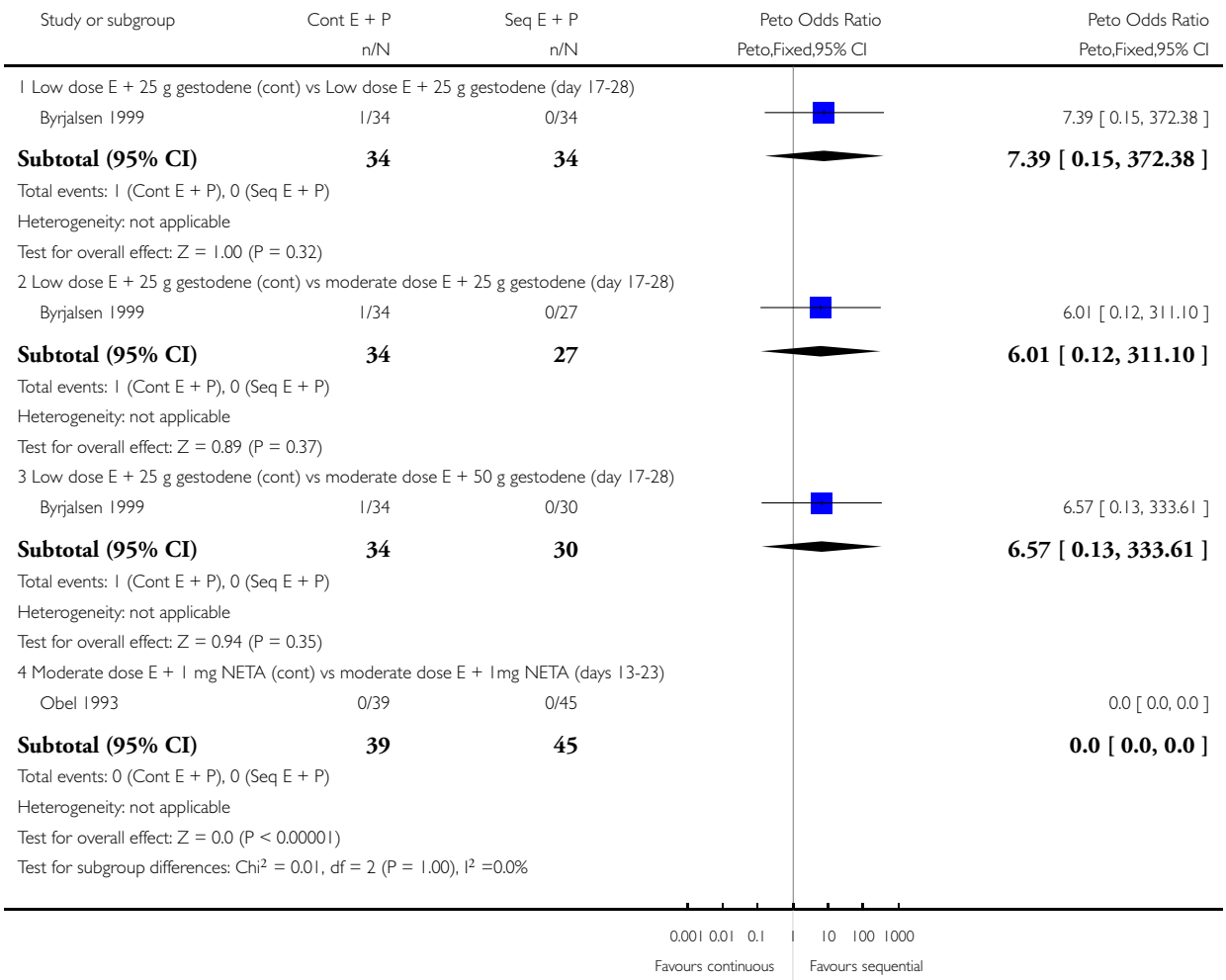


Analysis 6.5. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 5 Cumulative endometrial cancer at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 5 Cumulative endometrial cancer at 2 years



Analysis 6.6. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 6 Cumulative endometrial cancer at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 6 Cumulative endometrial cancer at 3 years

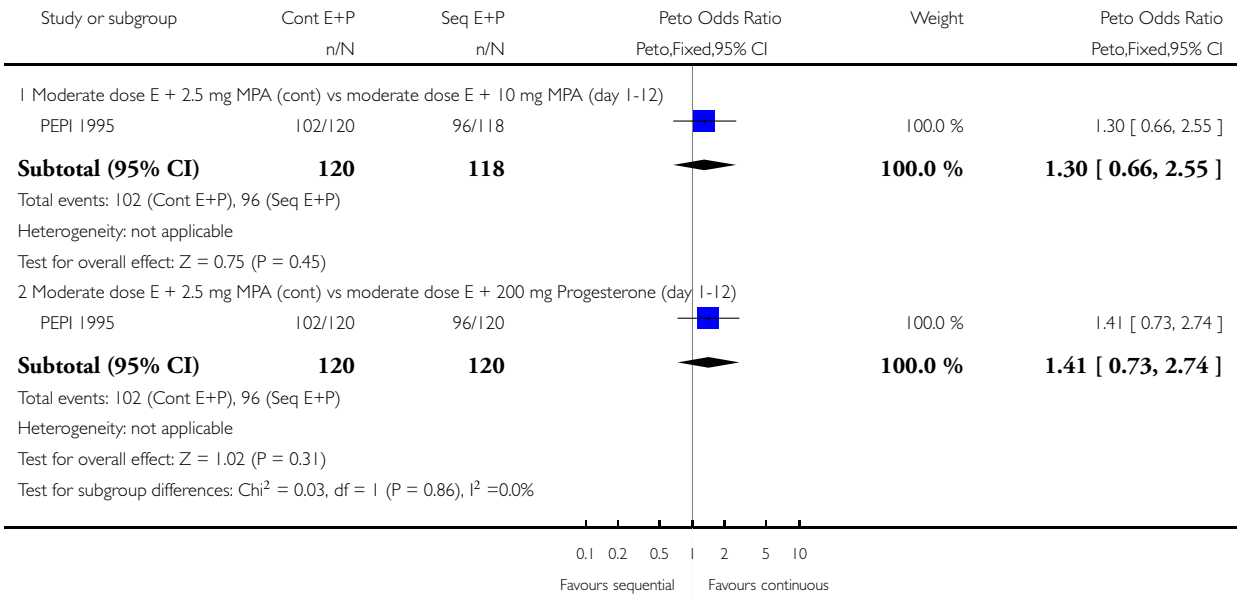
Study or subgroup	Cont E+P n/N	Seq E+P n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 10 mg MPA (day 1-12)				
PEPI 1995	0/120	0/118		0.0 [0.0, 0.0]
Subtotal (95% CI)	**120**	**118**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E+P), 0 (Seq E+P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 200 mg Progesterone (day 1-12)				
PEPI 1995	0/120	0/120		0.0 [0.0, 0.0]
Subtotal (95% CI)	**120**	**120**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E+P), 0 (Seq E+P)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**240**	**238**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont E+P), 0 (Seq E+P)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 6.7. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 7 Adherence to therapy.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 7 Adherence to therapy

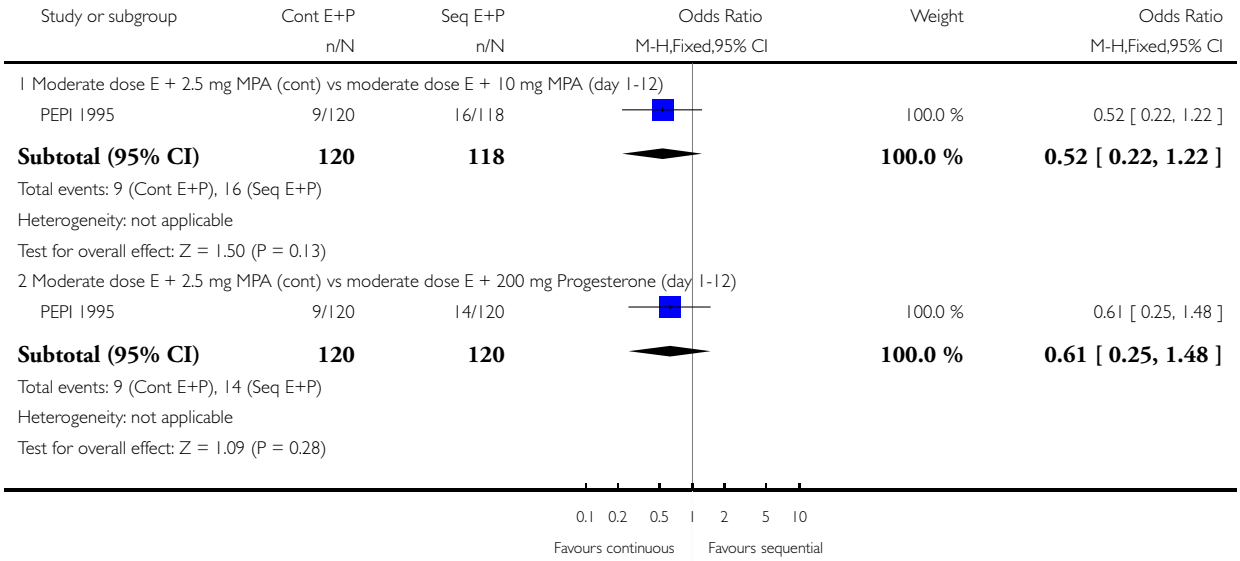


Analysis 6.8. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 8 Additional Investigations.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 8 Additional Investigations



Analysis 6.9. Comparison 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential), Outcome 9 Withdrawal due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 6 ESTROGEN + PROGESTOGEN (continuous) VS ESTROGEN + PROGESTOGEN (sequential)

Outcome: 9 Withdrawal due to adverse events

Study or subgroup	Cont E+P n/N	Seq E+P n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E + 1 mg NETA (cont) vs low dose E + 90 g NGM (days 4-6, 10-12 ....)					
Rozenberg 2001	24/217	29/221		100.0 %	0.82 [0.46, 1.47]
Subtotal (95% CI)	**217**	**221**		**100.0 %**	**0.82 [0.46, 1.47]**
Total events: 24 (Cont E+P), 29 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
2 Moderate dose E + 1 mg NETA (cont) vs low dose E + 180 g NGM (days 4-6, 10-12 ....)					
Rozenberg 2001	24/217	76/217		100.0 %	0.23 [0.14, 0.38]
Subtotal (95% CI)	**217**	**217**		**100.0 %**	**0.23 [0.14, 0.38]**
Total events: 24 (Cont E+P), 76 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.66 (P < 0.00001)					
3 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.35 mg NETA (day 4-6, 10-12 ...)					
Byrjalsen 2000	11/50	7/50		100.0 %	1.73 [0.61, 4.91]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**1.73 [0.61, 4.91]**
Total events: 11 (Cont E+P), 7 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
4 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 0.7 mg NETA (day 4-6, 10-12 ...)					
Byrjalsen 2000	11/50	7/50		100.0 %	1.73 [0.61, 4.91]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**1.73 [0.61, 4.91]**
Total events: 11 (Cont E+P), 7 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.03 (P = 0.30)					
5 Moderate dose E + 2.5 mg MPA (cont) vs moderate dose E + 5 mg MPA (day 14-25)					
Luciano 1993	2/12	4/12		100.0 %	0.40 [0.06, 2.77]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**0.40 [0.06, 2.77]**
Total events: 2 (Cont E+P), 4 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
6 Moderate dose E + 5mg MPA (cont) vs moderate dose E+ 5mg MPA (day 14-25)					
Luciano 1993	1/12	4/12		100.0 %	0.18 [0.02, 1.95]
Subtotal (95% CI)	**12**	**12**		**100.0 %**	**0.18 [0.02, 1.95]**

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Study or subgroup	Cont E+P n/N	Seq E+P n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total events: 1 (Cont E+P), 4 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
7 Moderate dose E + 1 mg NETA (cont) vs moderate dose E + 1mg NETA (days 13-23)					
Obel 1993	6/50	5/50		100.0 %	1.23 [0.35, 4.32]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**1.23 [0.35, 4.32]**
Total events: 6 (Cont E+P), 5 (Seq E+P)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.32 (P = 0.75)					

0.01 0.1 1 10 100

Favours continuous Favours sequential

Analysis 7.1. Comparison 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), Outcome 1 Endometrial hyperplasia at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons)

Outcome: 1 Endometrial hyperplasia at 1 year

Study or subgroup	Cont comb dose A n/N	Cont comb dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.5 mg DRSP vs low dose E + 1mg DRSP				
Archer 2005	0/227	0/231		0.0 [0.0, 0.0]
Subtotal (95% CI)	**227**	**231**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low dose E +2 mg DRSP vs Low dose E + 3 mg DRSP				
Archer 2005	1/227	0/231		7.52 [0.15, 379.06]
Subtotal (95% CI)	**227**	**231**		**7.52 [0.15, 379.06]**
Total events: 1 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.01 (P = 0.31)				
3 Low dose E + 0.125 mg TMG vs low dose E + 0.5 mg NETA				
Bouchard 2005	0/168	0/73		0.0 [0.0, 0.0]

0.001 0.01 0.1 1 10 100 1000

Favours Dose A Favours Dose B

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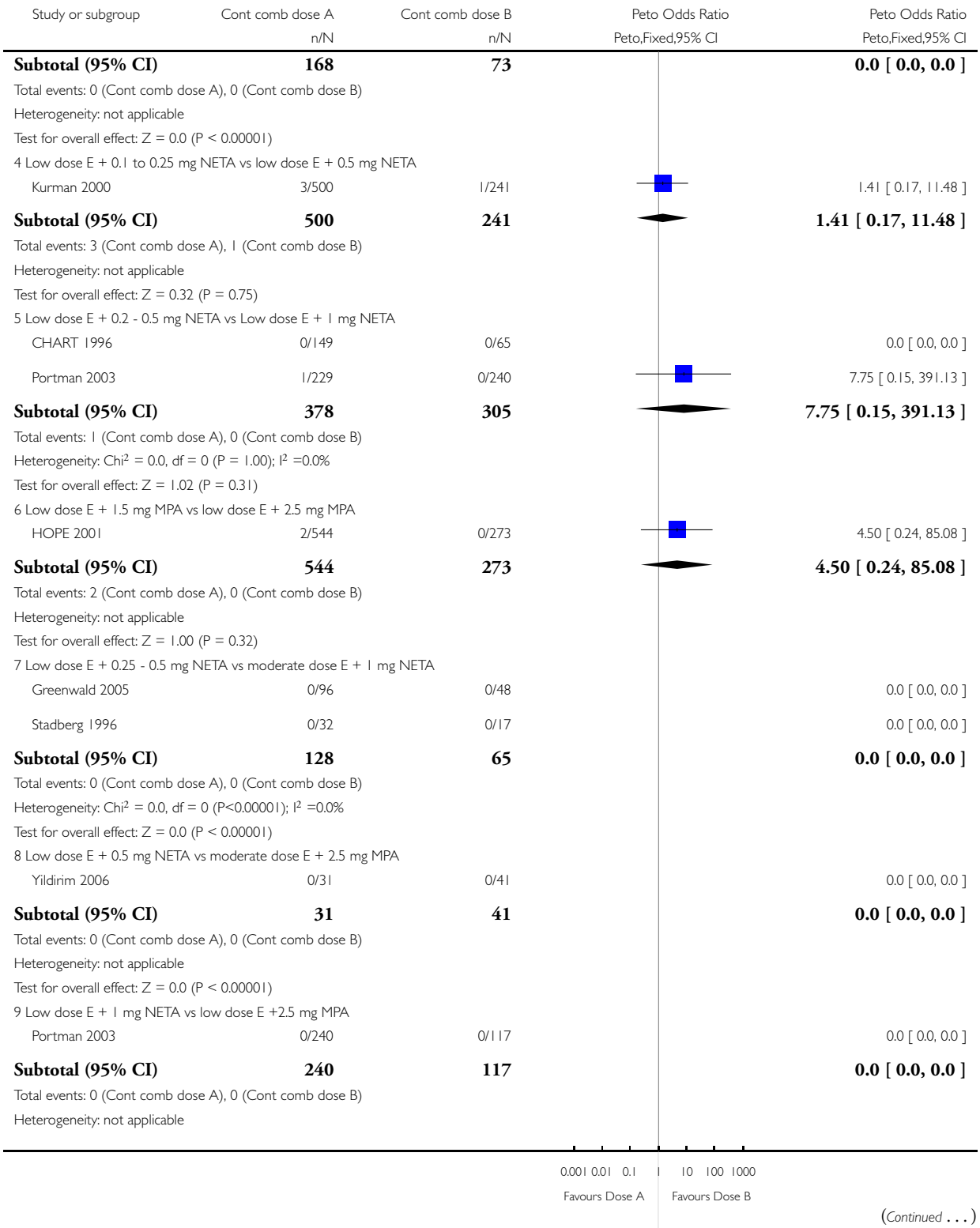

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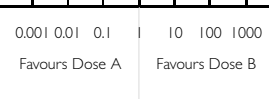
Study or subgroup	Cont comb dose A n/N	Cont comb dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: Z = 0.0 (P < 0.00001)				
10 Low dose E + 1.5 mg MPA vs mod dose E + 2.5 mg MPA				
HOPE 2001	2/544	0/278		4.54 [0.24, 85.12]
Subtotal (95% CI)	**544**	**278**		**4.54 [0.24, 85.12]**
Total events: 2 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.01 (P = 0.31)				
11 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA				
HOPE 2001	0/273	0/278		0.0 [0.0, 0.0]
Subtotal (95% CI)	**273**	**278**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
12 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA				
AinMelk 1996	0/26	0/27		0.0 [0.0, 0.0]
Subtotal (95% CI)	**26**	**27**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
13 Low dose E + 1 mg NETA vs moderate dose E + 1 mg NETA				
CHART 1996	0/65	0/71		0.0 [0.0, 0.0]
Subtotal (95% CI)	**65**	**71**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
14 Moderate dose E + 0.5 mg NETA vs moderate dose E + 2.5 mg MEGA				
Sporrong 1988	0/10	0/13		0.0 [0.0, 0.0]
Subtotal (95% CI)	**10**	**13**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
15 Moderate dose E + 0.5 mg NETA vs moderate dose E + 2.5 mg MPA				
Prestwood 2003	0/115	0/117		0.0 [0.0, 0.0]
Subtotal (95% CI)	**115**	**117**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
16 Moderate dose E + 1 mg NETA vs moderate dose E + 5 mg MEGA				
Sporrong 1988	0/14	0/11		0.0 [0.0, 0.0]



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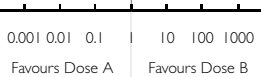
Study or subgroup	Cont comb dose A n/N	Cont comb dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**14**	**11**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
17 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA				
MSG 1994	2/279	0/274		7.28 [0.45, 116.76]
OGEN-Provera 1998	0/156	0/152		0.0 [0.0, 0.0]
Subtotal (95% CI)	**435**	**426**		**7.28 [0.45, 116.76]**
Total events: 2 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.40 (P = 0.16)				
18 Moderate dose E + 5 mg MPA vs moderate dose E + 10 mg MPA				
OGEN-Provera 1998	0/152	0/153		0.0 [0.0, 0.0]
Subtotal (95% CI)	**152**	**153**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
19 Mod - high dose E + 2.5 mg MPA vs mod - high dose E + 1 mg NETA				
Bruhat 2001	0/147	0/140		0.0 [0.0, 0.0]
Subtotal (95% CI)	**147**	**140**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
20 Mod - high dose E + 5 mg MPA vs mod - high dose E + 1 mg NETA				
Bruhat 2001	0/140	0/140		0.0 [0.0, 0.0]
Subtotal (95% CI)	**140**	**140**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
21 High dose E + 2 mg DNG vs moderate dose E + 1 mg NETA				
Graser 2000	0/141	0/136		0.0 [0.0, 0.0]
Subtotal (95% CI)	**141**	**136**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
22 High dose E + 3 mg DNG vs moderate dose E + 1 mg NETA				
Graser 2000	0/119	0/136		0.0 [0.0, 0.0]
Subtotal (95% CI)	**119**	**136**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb dose A), 0 (Cont comb dose B)				



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Study or subgroup	Cont comb dose A n/N	Cont comb dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 1.34, df = 5 (P = 0.93), I^2 =0.0%				

0.001 0.01 0.1 1 10 100 1000

Favours Dose A Favours Dose B

Analysis 7.2. Comparison 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons)

Outcome: 2 Cumulative endometrial hyperplasia at 2 years

Study or subgroup	Cont comb Dose A n/N	Cont comb Dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 1 mg DRSP vs low dose E + 2 mg DRSP				
Warming 2004	0/39	0/49		0.0 [0.0, 0.0]
Subtotal (95% CI)	**39**	**49**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low dose E + 2mg DRSP vs low dose E + 3 mg DRSP				
Warming 2004	0/49	0/45		0.0 [0.0, 0.0]
Subtotal (95% CI)	**49**	**45**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Low dose E + 0.125 mg TMG vs moderate dose E + 1 mg NETA				
Bouchard 2005	0/108	0/62		0.0 [0.0, 0.0]
Subtotal (95% CI)	**108**	**62**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Low dose E + 0.2 - 0.5mg NETA vs Low dose E + 1 mg NETA				
CHART 1996	0/65	0/65		0.0 [0.0, 0.0]

0.001 0.01 0.1 1 10 100 1000

Favours Dose A Favours Dose B

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Study or subgroup	Cont comb Dose A n/N	Cont comb Dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**65**	**65**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
5 Low dose E + 1.5 mg MPA vs low dose E + 2.5 mg MPA				
HOPE 2001	0/144	0/66		0.0 [0.0, 0.0]
Subtotal (95% CI)	**144**	**66**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
6 Low dose E + 2 mg MPA vs moderate dose E + 2mg MPA				
Wu 2002	0/69	2/73		0.14 [0.01, 2.28]
Subtotal (95% CI)	**69**	**73**		**0.14 [0.01, 2.28]**
Total events: 0 (Cont comb Dose A), 2 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.38 (P = 0.17)				
7 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA				
HOPE 2001	0/66	0/62		0.0 [0.0, 0.0]
Subtotal (95% CI)	**66**	**62**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
8 Low dose E + 2.5 mg MPA vs moderate dose E + 2.5 mg MPA				
AinMelk 1996	0/26	0/27		0.0 [0.0, 0.0]
Subtotal (95% CI)	**26**	**27**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
9 Low dose E + 1.5 mg MPA vs moderate dose E + 2.5 mg MPA				
HOPE 2001	0/144	0/62		0.0 [0.0, 0.0]
Subtotal (95% CI)	**144**	**62**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
10 Low dose E + 1 mg NETA vs moderate dose E + 1 mg NETA				
CHART 1996	0/65	0/71		0.0 [0.0, 0.0]
Subtotal (95% CI)	**65**	**71**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
11 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA				

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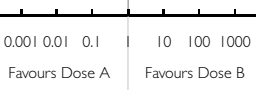
Study or subgroup	Cont comb Dose A n/N	Cont comb Dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Heikkinen 2000	0/69	0/70		0.0 [0.0, 0.0]
Nand 1995	0/7	0/4		0.0 [0.0, 0.0]
OGEN-Provera 1998	0/140	0/137		0.0 [0.0, 0.0]
Subtotal (95% CI)	**216**	**211**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
12 Moderate dose E + 5 mg MPA vs moderate dose E + 10 mg MPA				
Nand 1995	0/4	0/8		0.0 [0.0, 0.0]
OGEN-Provera 1998	0/137	0/138		0.0 [0.0, 0.0]
Subtotal (95% CI)	**141**	**146**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
13 Moderate to high dose E + 5 mg MPA vs high dose E + 1 mg NETA				
Mattsson 2004	0/82	0/81		0.0 [0.0, 0.0]
Subtotal (95% CI)	**82**	**81**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
14 Moderate to high dose E + 2.5 mg MPA vs high dose E + 1 mg NETA				
Mattsson 2004	0/92	0/81		0.0 [0.0, 0.0]
Subtotal (95% CI)	**92**	**81**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
15 Moderate to high dose E + 2.5 mg MPA vs moderate to high dose E + 5 mg MPA				
Heikkinen 2000	0/70	0/70		0.0 [0.0, 0.0]
Subtotal (95% CI)	**70**	**70**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
16 High dose E + 2.5 mg MPA vs high dose E + 5 mg MPA				
Heikkinen 2000	0/70	0/70		0.0 [0.0, 0.0]
Subtotal (95% CI)	**70**	**70**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				



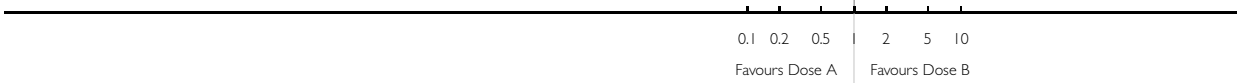
Analysis 7.3. Comparison 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), Outcome 3 Endometrial cancer at one year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons)

Outcome: 3 Endometrial cancer at one year

Study or subgroup	Cont comb Dose A n/N	Cont comb Dose B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.1 to 0.25 mg NETA vs low dose E + 0.5 mg NETA				
Kurman 2000	0/500	0/241		0.0 [0.0, 0.0]
Subtotal (95% CI)	**500**	**241**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose E + 2.5 mg MPA vs moderate dose E + 5 mg MPA				
MSG 1994	0/279	0/274		0.0 [0.0, 0.0]
Subtotal (95% CI)	**279**	**274**		**0.0 [0.0, 0.0]**
Total events: 0 (Cont comb Dose A), 0 (Cont comb Dose B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

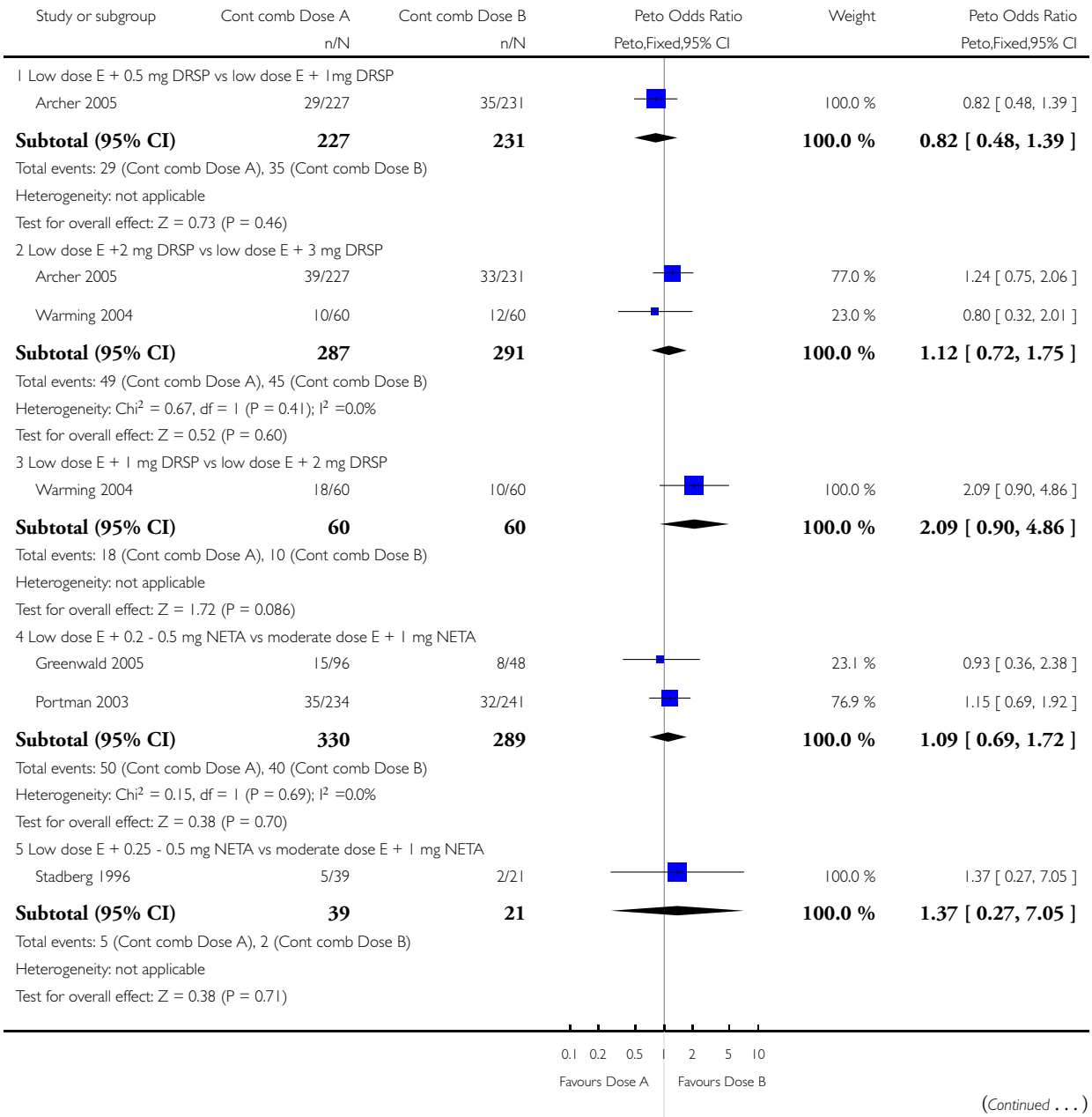


Analysis 7.4. Comparison 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons), Outcome 4 Withdrawal due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 7 CONTINUOUS COMBINED ESTROGEN + PROGESTOGEN (dose comparisons)

Outcome: 4 Withdrawal due to adverse events



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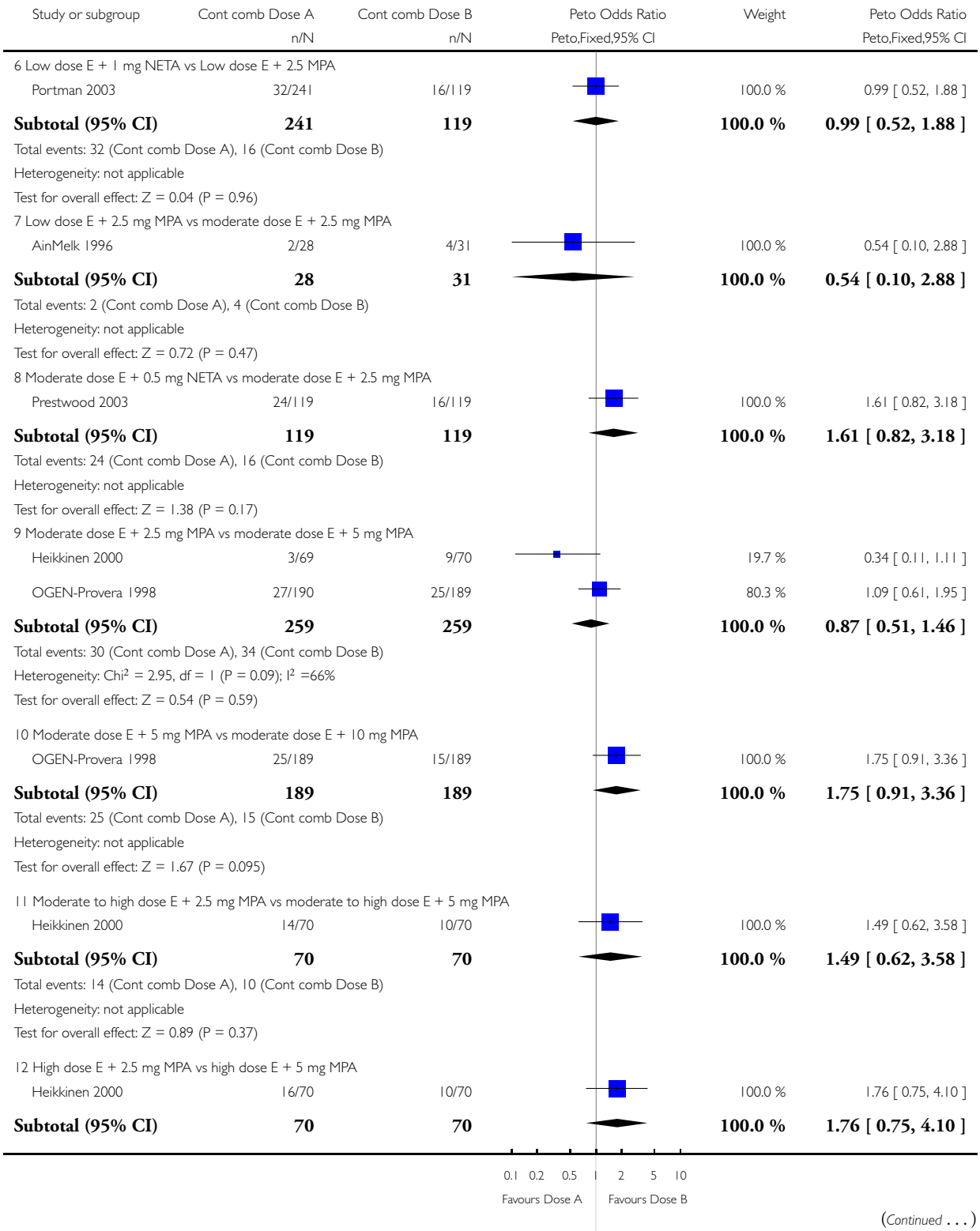

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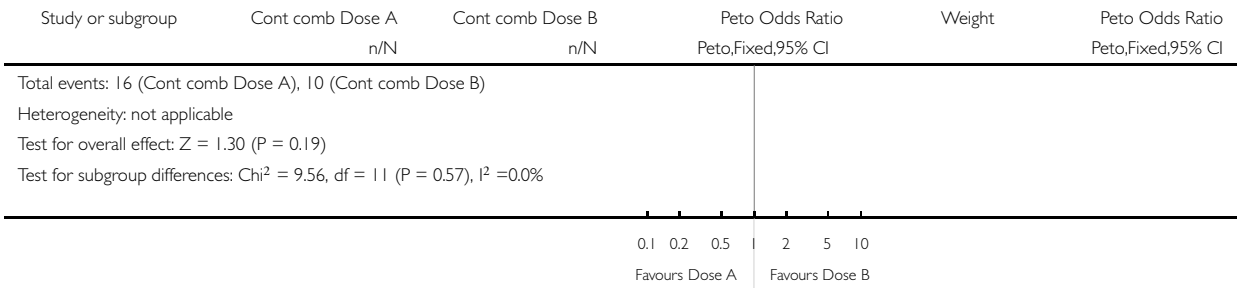
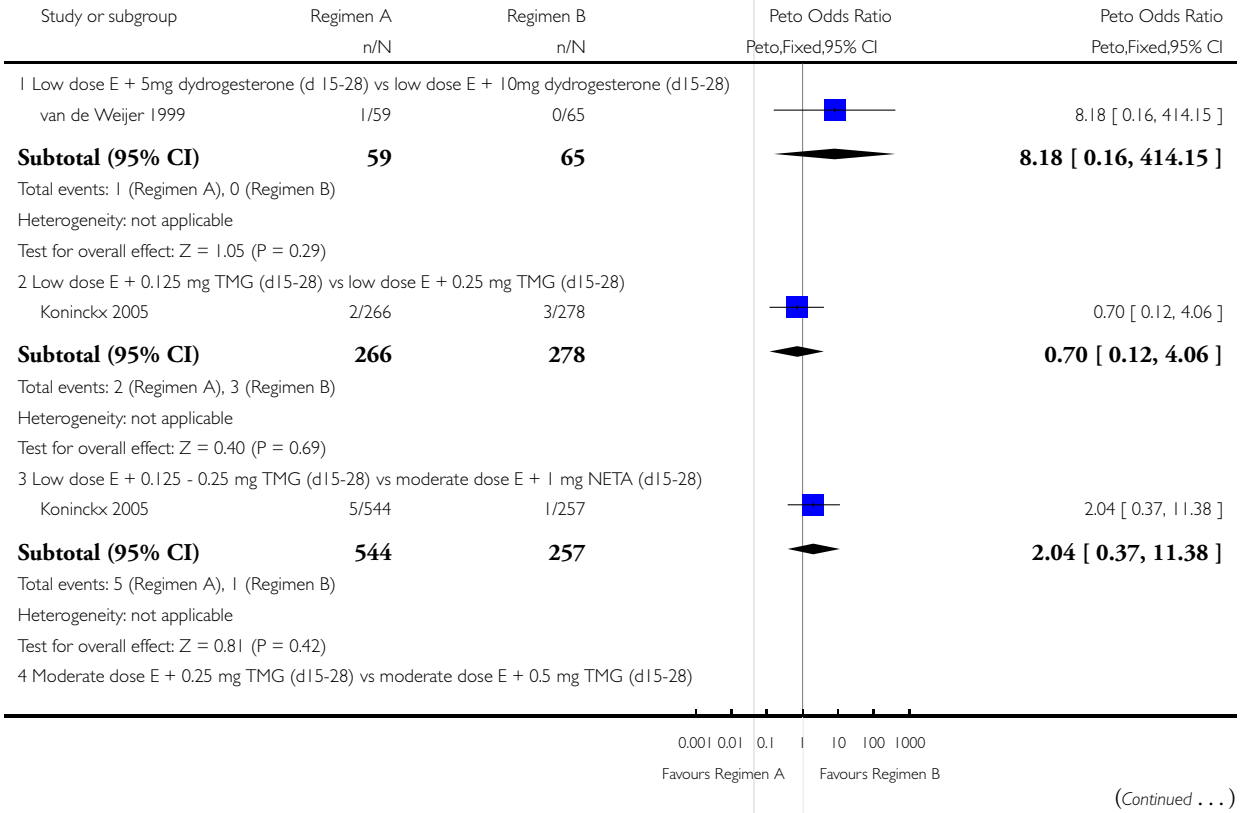


Analysis 8.1. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 1 Endometrial hyperplasia at 1 year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 1 Endometrial hyperplasia at 1 year



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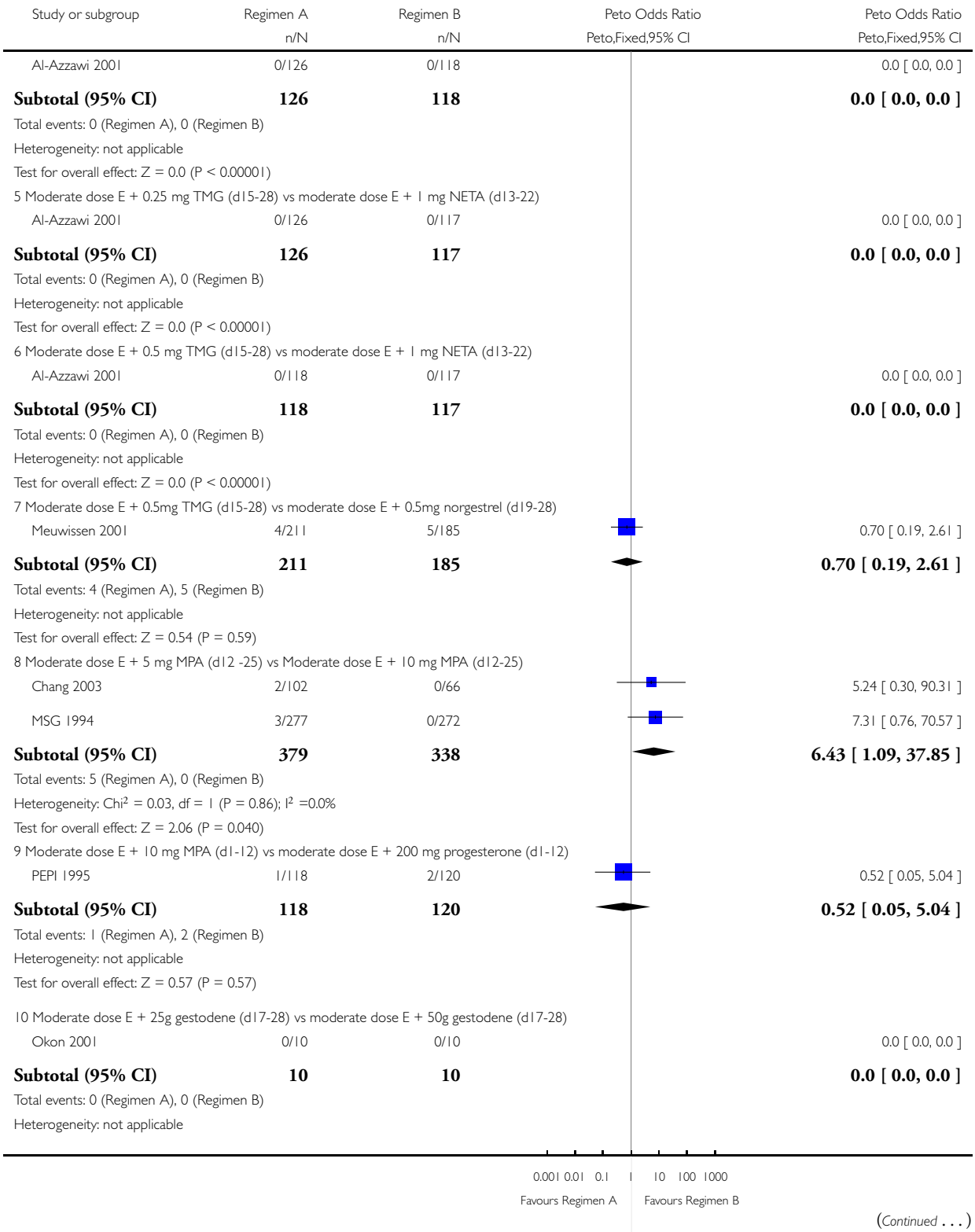

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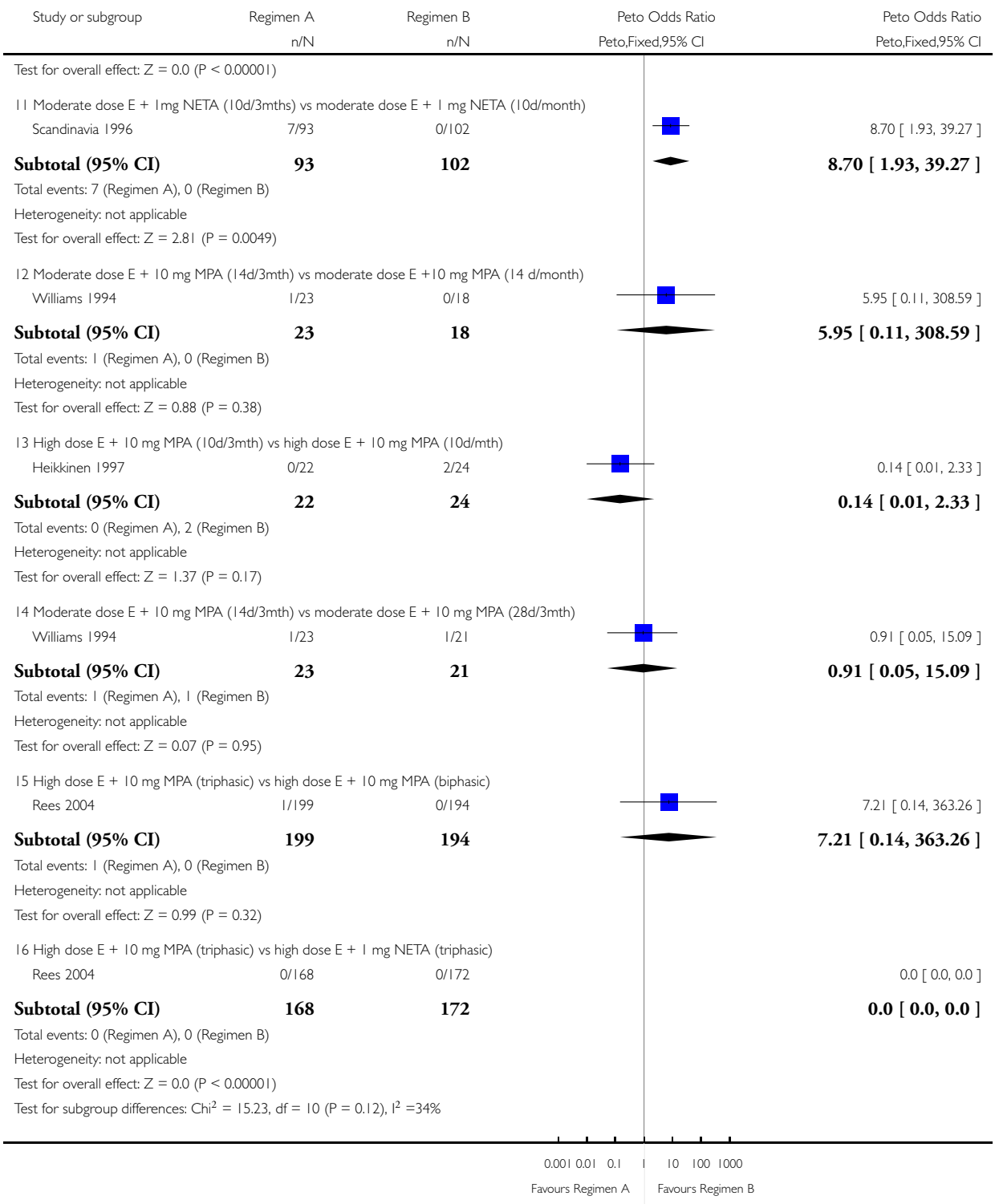

Analysis 8.2. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 2 Cumulative endometrial hyperplasia at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 2 Cumulative endometrial hyperplasia at 2 years

Study or subgroup	Regimen A n/N	Regimen B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.35mg NETA (d 4-6, 10-12 ....) vs Moderate dose E + 0.7mg NETA (d 4-6, 10-12 ....)				
Byrjalsen 2000	0/32	0/26		0.0 [0.0, 0.0]
Subtotal (95% CI)	**32**	**26**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low dose E + 5mg DYG (d15-28) vs low dose E + 10 mg DYG (d15-28)				
Ferenczy 2002	0/100	0/95		0.0 [0.0, 0.0]
Subtotal (95% CI)	**100**	**95**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Moderate dose E + 10mg DYG (d15-28) vs moderate dose E + 20 mg DYG (d15-28)				
Ferenczy 2002	0/88	0/96		0.0 [0.0, 0.0]
Subtotal (95% CI)	**88**	**96**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)				
PEPI 1995	4/118	3/120		1.36 [0.30, 6.12]
Subtotal (95% CI)	**118**	**120**		**1.36 [0.30, 6.12]**
Total events: 4 (Regimen A), 3 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.41 (P = 0.69)				
5 High dose E + 10 mg MPA (10d/3mths) vs high dose E +10 mg MPA (10d/mth)				
Heikkinen 1997	0/21	3/23		0.13 [0.01, 1.37]
Subtotal (95% CI)	**21**	**23**		**0.13 [0.01, 1.37]**
Total events: 0 (Regimen A), 3 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.69 (P = 0.090)				
6 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/mth)				
Scandinavia 1996	7/93	1/102		5.24 [1.27, 21.51]
Subtotal (95% CI)	**93**	**102**		**5.24 [1.27, 21.51]**

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Study or subgroup	Regimen A n/N	Regimen B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 7 (Regimen A), 1 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.30 (P = 0.022)				
Test for subgroup differences: Chi² = 7.11, df = 2 (P = 0.03), I² =72%				

Analysis 8.3. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 3 Cumulative endometrial hyperplasia at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 3 Cumulative endometrial hyperplasia at 3 years

Study or subgroup	Regimen A n/N	Regimen B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)					
PEPI 1995	6/118	6/120		100.0 %	1.02 [0.32, 3.24]
Subtotal (95% CI)	**118**	**120**		**100.0 %**	**1.02 [0.32, 3.24]**
Total events: 6 (Regimen A), 6 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
2 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/mth)					
Scandinavia 1996	14/93	2/102		100.0 %	5.64 [2.03, 15.65]
Subtotal (95% CI)	**93**	**102**		**100.0 %**	**5.64 [2.03, 15.65]**
Total events: 14 (Regimen A), 2 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.32 (P = 0.00090)					
Test for subgroup differences: Chi² = 4.72, df = 1 (P = 0.03), I² =79%					

Analysis 8.4. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 4 Endometrial cancer at one year.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

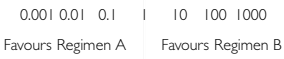
Outcome: 4 Endometrial cancer at one year

Study or subgroup	Regimen A n/N	Regimen B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.125 mg TMG (d15-28) vs low dose E + 0.25 mg TMG (d15-28)				
Koninckx 2005	0/266	0/278		0.0 [0.0, 0.0]
Subtotal (95% CI)	**266**	**278**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low dose E + 0.125 - 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d15-28)				
Koninckx 2005	0/544	1/257		0.04 [0.00, 2.95]
Subtotal (95% CI)	**544**	**257**		**0.04 [0.00, 2.95]**
Total events: 0 (Regimen A), 1 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.45 (P = 0.15)				
3 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 0.5 mg TMG (d15-28)				
Al-Azzawi 2001	0/126	0/118		0.0 [0.0, 0.0]
Subtotal (95% CI)	**126**	**118**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Moderate dose E + 0.25 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)				
Al-Azzawi 2001	0/126	1/117		0.13 [0.00, 6.33]
Subtotal (95% CI)	**126**	**117**		**0.13 [0.00, 6.33]**
Total events: 0 (Regimen A), 1 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.04 (P = 0.30)				
5 Moderate dose E + 0.5 mg TMG (d15-28) vs moderate dose E + 1 mg NETA (d13-22)				
Al-Azzawi 2001	0/118	1/117		0.13 [0.00, 6.76]
Subtotal (95% CI)	**118**	**117**		**0.13 [0.00, 6.76]**
Total events: 0 (Regimen A), 1 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.00 (P = 0.32)				
6 Moderate dose E + 0.5mg TMG (d15-28) vs moderate dose E + 0.5mg norgestrel (d19-28)				
Meuwissen 2001	0/211	1/185		0.12 [0.00, 5.98]
Subtotal (95% CI)	**211**	**185**		**0.12 [0.00, 5.98]**

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Regimen A n/N	Regimen B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 0 (Regimen A), 1 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.07 (P = 0.29)				
7 Moderate dose E + 5 mg MPA (d12 -25) vs Moderate dose E + 10 mg MPA (d12-25)				
Chang 2003	0/102	0/66		0.0 [0.0, 0.0]
MSG 1994	0/277	1/272		0.13 [0.00, 6.70]
Subtotal (95% CI)	**379**	**338**		**0.13 [0.00, 6.70]**
Total events: 0 (Regimen A), 1 (Regimen B)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.01 (P = 0.31)				
Test for subgroup differences: Chi^2 = 0.20, df = 4 (P = 1.00), I^2 =0.0%				



Analysis 8.5. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 5 Cumulative endometrial cancer at 2 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 5 Cumulative endometrial cancer at 2 years

Study or subgroup	Regimen A n/N	Regimen B n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Low dose E + 25g gestodene vs moderate dose E + 25 g gestodene				
Byrjalsen 1999	0/34	0/27		0.0 [0.0, 0.0]
Subtotal (95% CI)	**34**	**27**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Low dose E + 5mg DYG (d15-28) vs low dose E + 10 mg DYG (d15-28)				
Ferenczy 2002	1/100	0/95		2.88 [0.12, 71.56]
Subtotal (95% CI)	**100**	**95**		**2.88 [0.12, 71.56]**
Total events: 1 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				

(*Continued* . . .)

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Study or subgroup	Regimen A n/N	Regimen B n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.65 (P = 0.52)				
3 Moderate dose E + 10mg DYG (d15-28) vs moderate dose E + 20 mg DYG (d15-28)				
Ferenczy 2002	0/88	2/96		0.21 [0.01, 4.51]
Subtotal (95% CI)	**88**	**96**		**0.21 [0.01, 4.51]**
Total events: 0 (Regimen A), 2 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.99 (P = 0.32)				
4 Moderate dose E + 25ug gestodene vs moderate dose E + 50ug gestodene				
Byrjalsen 1999	0/27	0/30		0.0 [0.0, 0.0]
Subtotal (95% CI)	**27**	**30**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 8.6. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 6 Cumulative endometrial cancer at 3 years.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 6 Cumulative endometrial cancer at 3 years

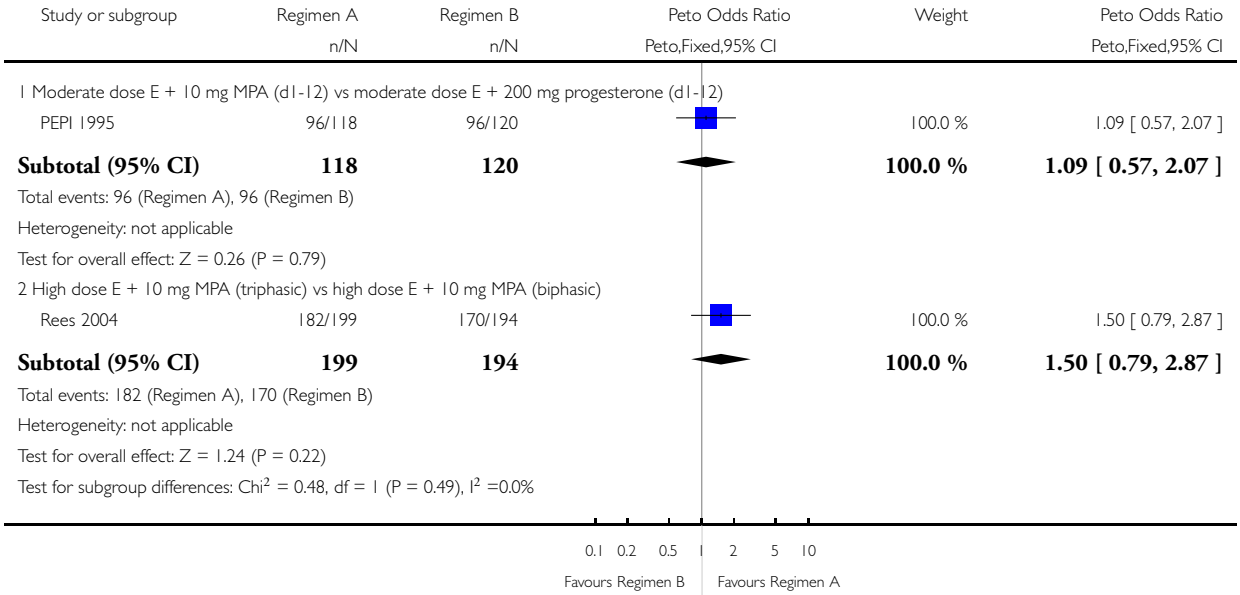
Study or subgroup	Regimen A n/N	Regimen B n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)				
PEPI 1995	0/118	0/120		0.0 [0.0, 0.0]
Subtotal (95% CI)	**118**	**120**		**0.0 [0.0, 0.0]**
Total events: 0 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Moderate dose E + 1mg NETA (10d/3mths) vs moderate dose E + 1 mg NETA (10d/mth)				
Scandinavia 1996	1/93	0/102		3.32 [0.13, 82.62]
Subtotal (95% CI)	**93**	**102**		**3.32 [0.13, 82.62]**
Total events: 1 (Regimen A), 0 (Regimen B)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.73 (P = 0.46)				

Analysis 8.7. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 7 Adherence to therapy.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 7 Adherence to therapy



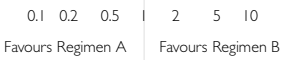
Analysis 8.8. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 8 Additional Investigations.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 8 Additional Investigations

Study or subgroup	Regimen A n/N	Regimen B n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate dose E + 10 mg MPA (d1-12) vs moderate dose E + 200 mg progesterone (d1-12)					
PEPI 1995	16/118	14/120		100.0 %	1.19 [0.55, 2.56]
Total (95% CI)	**118**	**120**		**100.0 %**	**1.19 [0.55, 2.56]**
Total events: 16 (Regimen A), 14 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.44 (P = 0.66)					



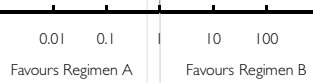
Analysis 8.9. Comparison 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons), Outcome 9 Withdrawals due to adverse events.

Review: Hormone therapy in postmenopausal women and risk of endometrial hyperplasia

Comparison: 8 SEQUENTIAL ESTROGEN + PROGESTOGEN (dose/regimen comparisons)

Outcome: 9 Withdrawals due to adverse events

Study or subgroup	Regimen A n/N	Regimen B n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Low dose E + 0.35mg NETA (d 4-6, 10-12 ....) vs Moderate dose E + 0.7mg NETA (d 4-6, 10-12 ....)					
Byrjalsen 2000	7/50	14/50		100.0 %	0.43 [0.17, 1.13]
Subtotal (95% CI)	**50**	**50**		**100.0 %**	**0.43 [0.17, 1.13]**
Total events: 7 (Regimen A), 14 (Regimen B)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.71 (P = 0.087)					
2 Low dose E + 5mg DYG (d15-28) vs low dose E + 10 mg DYG (d15-28)					
Ferenczy 2002	17/117	17/114		100.0 %	0.97 [0.47, 2.01]
Subtotal (95% CI)	**117**	**114**		**100.0 %**	**0.97 [0.47, 2.01]**
Total events: 17 (Regimen A), 17 (Regimen B)					



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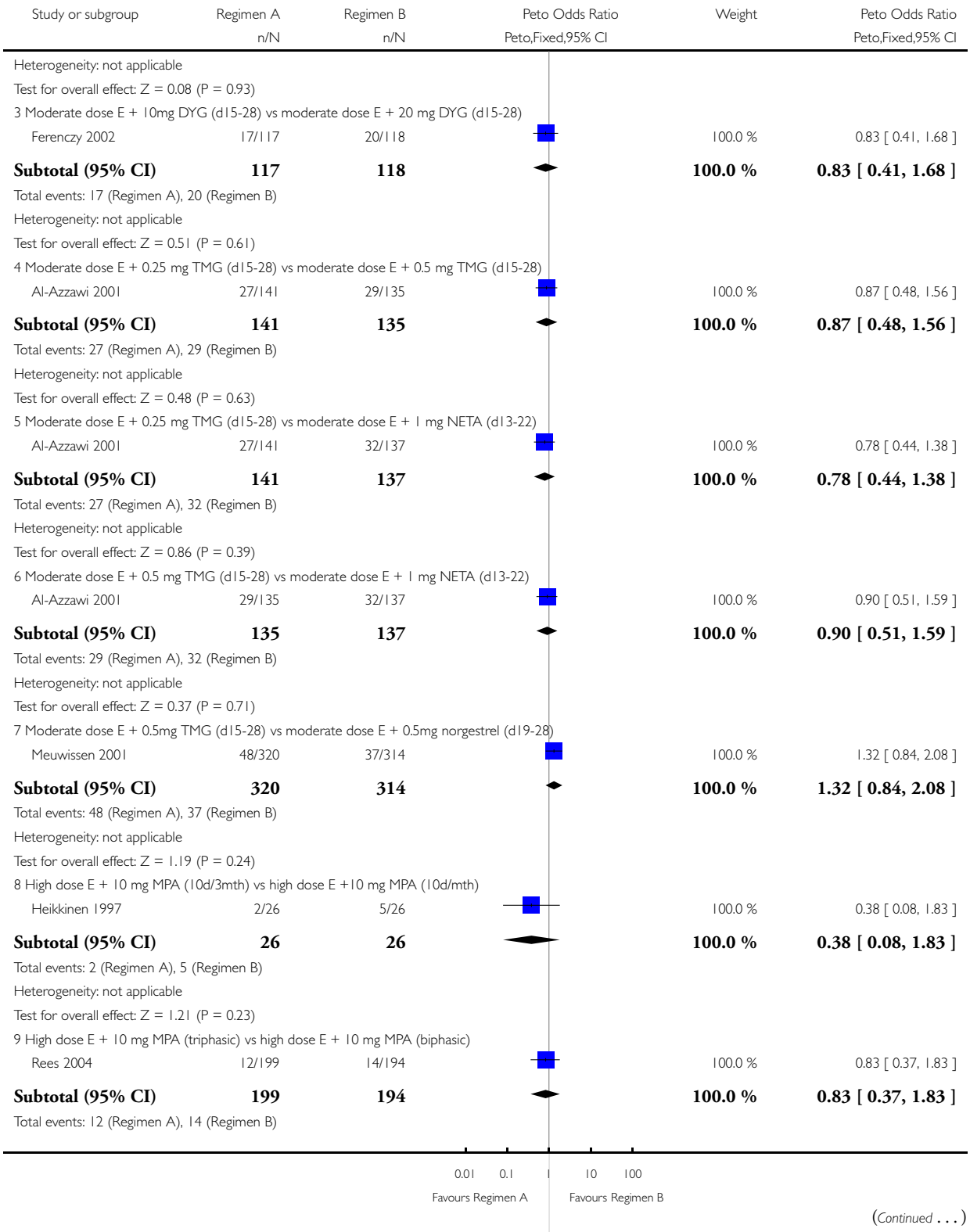

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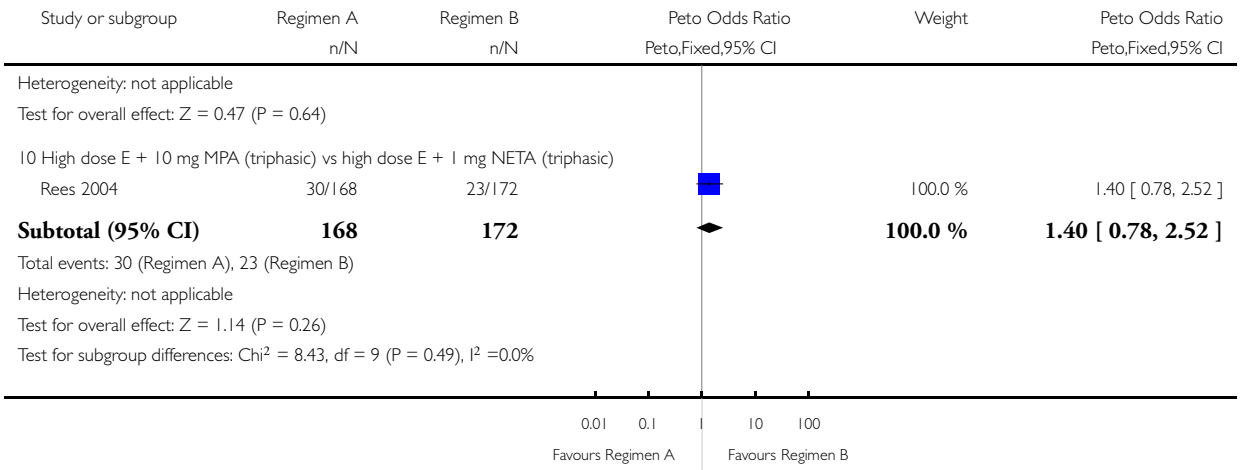

ADDITIONAL TABLES

Table 1. Classification of Estrogen dosages

Estrogen	Low Dose (mg/day)	Moderate Dose (mg/d)	High Dose (mg/day)
Conjugated equine estrogens (CEE)	0.15, 0.3, 0.4	0.625	1.25
Estrone sulphate (POS)	0.3, 0.625	1.25, 1.5	2.5
Ethinyl Estradiol (EE)	< 0.010	0.010	>0.010
17 Beta estradiol (17βE2)	0.5, 1.0	1.5, 2	4
Estradiol valerate	0.5	1	2
Esterified estrogens	0.3	0.625	1.25

Table 2. Continuous HT - the lowest 'safe' dose; minimum progestogen dose for various estrogen types and doses compared to unopposed E

	E Dose	P Dose	RCT evidence	Events E+P	Events E alone	Duration	Allocation concealment
Low dose E	5 µg EE	1 mg NETA	CHART 1996	0/65	4/221	2 years	Adequate
	1 mg 17βE2	0.5 DRSP	Archer 2005	0/231	4/113	1 year	B

Table 2. Continuous HT - the lowest 'safe' dose; minimum progestogen dose for various estrogen types and doses compared to unopposed E (*Continued*)

	1 mg 17βE2	0.1 mg NETA	Kurman 2000	2/249	36/247	1 year	Adequate
	0.3 -0.45 mg CEE	1.5 MPA	HOPE 2001	0/144	6/65	2 years	Adequate
	0.45 mg CEE	2.5 MPA	HOPE 2001	0/66	6/65	2 years	Adequate
Mod dose E	0.625 mg CEE	2.5 mg MPA	HOPE 2001; PEPI 1995	1/182	69/174	2 years	Adequate;Adequate
	0.625 mg CEE	5 mg MPA	MSG 1994	2/279	57/283	1 year	Adequate
	10 µg EE	1 mg NETA	CHART 1996	0/65	10/18*	2 years	Adequate

*this group stopped hormone therapy early due to high rate of endometrial hyperplasia

Table 3. Sequential HT - the lowest 'safe' dose of progestogen for various types and doses of estrogen compared to unopposed E

	E Dose	P Dose	RCT evidence	Events E+P	Events E alone	Duration	Allocation concealment
Low dose E	1 mg 17βE2	30 µg NGM intermittent**	Corson 1999	16/260	74/265	1 year	Unclear
Moderate dose E	0.625 mg CEE	5 mg MPA (11-12 d/mth)	Gelfand 1989; MSG 1994	4/310	65/310	1 year	Adequate; Adequate
	0.625 mg CEE	10 mg MPA (12 d/mth)	PEPI 1995	6/118	74/119	3 years	Adequate
	0.625 mg CEE	200 mg progesterone (12d/mth)	PEPI 1995	6/120	74/119	3 years	Adequate
	0.625 mg CEE	10 mg MPA (14d/mth)	MSG 1994	0/272	57/283	1 year	Adequate
High dose E	1.25 mg CEE	5 mg MPA	Gelfand 1989	13/23	1/10	1 year	Adequate

** 3 days E+P followed by 3 days unopE only, repeated

Table 4. Continuous HT - the lowest 'safe' dose: minimum progestogen doses for various types and doses of estrogen compared to placebo

	E Dose	P Dose	RCT evidence	Events E+P	Events placebo	Duration	Allocation concealment
Low dose E	5 µg EE	1 mg NETA	CHART 1996; Portman 2003	1/378	1/198	1 year	Adequate;Adequate
	5 µg EE	1 mg NETA	CHART 1996	0/130	1/59	2 years	Adequate
	0.3 -0.45 mg CEE	1.5 mg MPA	HOPE 2001	0/144	0/61	2 years	Adequate
	1 mg 17βE2	1 mg drospirinone	Warming 2004	0/39	0/47	2 years	Adequate
	1 mg 17βE2	25 µg Gestodene	Byrjalsen 1999	0/34	0/43	2 years	Unclear
Moderate dose E	10 µg EE	1 mg NETA	CHART 1996	0/65	1/59	2 years	Adequate
	2 mg 17βE2	1 mg NETA	Byrjalsen 2000; Greenwald 2005; Obel 1993	0/117	1/118	2 years	Adequate; Unclear; Unclear
	0.625 mg CEE	2.5 mg MPA	PEPI 1995; HOPE 2001	1/182	0/180	2 years	Adequate; Adequate
	0.625 mg CEE	2.5 mg MPA	PEPI 1995	1/120	2/119	3 years	Adequate

Table 5. Sequential HT - the lowest 'safe' dose of progestogen for various doses and types of estrogen compared to placebo

	E Dose	P Dose	RCT evidence	Events E+P	Events placebo	Duration	Allocation concealment
Low dose E	0.25 mg 17βE2	100 mg progesterone (15 d/6mths)	Prestwood 2003	1/59	1/57	3 years	Adequate
	1 mg 17βE2	5 mg dydrogesterone (14 d/mth)	Ferenczy 2002	0/100	0/63	2 years	Unclear
	1 mg 17βE2	25 µg gestodene (12d/	Byrjalsen 1999	0/34	0/43	2 years	Unclear

Table 5. Sequential HT - the lowest 'safe' dose of progestogen for various doses and types of estrogen compared to placebo (*Continued*)

		mth)					
	0.75 mg POS	0.35 mg NETA (intermittent)**	Byrjalsen 2000	0/32	0/25	2 years	Adequate
Moderate dose E	1.5 mg 17βE2	150 µg desogestrel (14d/mth)	Byrjalsen 1992	0/20	0/18	2 years	Unclear
	1.5 mg POS***	0.7 mg NETA (intermittent)**	Byrjalsen 2000	0/26	0/25	2 years	Adequate
	0.625 mg CEE	200 mg progesterone (12d/mth)	PEPI 1995	6/120	2/119	3 years	Adequate
	2 mg 17βE2	1 mg NETA (10d/mth)	Obel 1993	0/45	0/45	2 years	Unclear
	2 mg 17βE2	10 mg dydrogesterone (14d/mth)	Ferenczy 2002	0/88	0/63	2 years	Unclear
	2 mg 17βE2	25 µg gestodene (12d/mth)	Byrjalsen 1999	0/27	0/43	2 years	Unclear
Hi dose E	2 mg E2V	10 mg MPA (10d/mth)	Heikkinen 1997; Byrjalsen 1992	3/41	1/43	2 years	Unclear; Unclear
	2 mg E2V	10 mg MPA (14d/6mths)-long cycle	Heikkinen 1997	0/21	1/25	2 years	Unclear

**3 days E+P followed by 3 days E only, repeated
*** Piperazine estrone sulphate

APPENDICES

Appendix 1. Medline search strategy

1. exp climacteric/ or exp menopause/
2. (climacter$ or menopaus$).tw.
3. (postmenopaus$ or post-menopaus$ or post menopaus$).tw.
4. or/1-3
5. exp estrogens/
6. hormone replacement therapy/ or estrogen replacement therapy/
7. exp Progestins/
8. (hormone replacement therapy or HRT).tw.
9. (estrogen$ or progest$).tw.
10. endometrial hyperplasia/
11. (endometri$ adj5 hyperplasia).tw.
12. (endometri$ adj5 carcinoma).tw.
13. (endometri$ adj5 (biops$ or histology)).tw.
14. (hysteroscop$ or hysterectomy).tw.
15. (adherence or compliance).tw.
16. randomized controlled trial.pt.
17. controlled clinical trial.pt.
18. Randomized Controlled Trials/
19. Random allocation/
20. Double-blind method/
21. Single-blind method/
22. or/16-21
23. clinical trial.pt.
24. exp clinical trials/
25. (clin$ adj25 trial$).ti,ab,sh.
26. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
27. Placebos/
28. placebo$.ti,ab,sh.
29. random$.ti,ab,sh.
30. Research design/
31. or/23-30
32. animal/ not (human/ and animal/)
33. 22 or 31
34. 33 not 32
35. review.pt.
36. letter.pt.
37. or/5-9
38. or/10-15
39. 4 and 37 and 38
40. 39 and 34
41. 40 not (35 or 36)

Appendix 2. Embase search strategy

1. exp climacteric/ or exp menopause/
2. (climacter$ or menopaus$).tw.
3. (postmenopaus$ or post-menopaus$ or post menopaus$).tw.
4. or/1-3
5. exp estrogens/
6. hormone replacement therapy/ or estrogen replacement therapy/
7. exp Progestins/
8. (hormone replacement therapy or HRT).tw.
9. (estrogen$ or progest$).tw.
10. endometrial hyperplasia/
11. (endometri$ adj5 hyperplasia).tw.
12. (endometri$ adj5 carcinoma).tw.
13. (endometri$ adj5 (biops$ or histology)).tw.
14. (hysteroscop$ or hysterectomy).tw.
15. (adherence or compliance).tw.
16. Controlled study/ or randomized controlled trial/
17. double blind procedure/
18. single blind procedure/
19. crossover procedure/
20. drug comparison/
21. placebo/
22. random$.ti,ab,hw,tn,mf.
23. latin square.ti,ab,hw,tn,mf.
24. crossover.ti,ab,hw,tn,mf.
25. cross-over.ti,ab,hw,tn,mf.
26. placebo$.ti,ab,hw,tn,mf.
27. ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
28. (comparative adj5 trial$).ti,ab,hw,tn,mf.
29. (clinical adj5 trial$).ti,ab,hw,tn,mf.
30. or/16-29
31. nonhuman/
32. animal/ not (human/ and animal/)
33. or/31-32
34. 30 not 33
35. review.pt.
36. letter.pt.
37. or/5-9
38. or/10-15
39. 4 and 37 and 38
40. (39 and 34) not (35 or 36)

Appendix 3. PsychInfo search strategy

1. exp Menopause/
2. (climacteric or menopaus$ or postmenopaus$).tw.
3. 1 or 2
4. exp ESTROGENS/
5. exp Hormone Therapy/
6. hormone replacement therap$.mp. or hormone therap$.tw. [mp=title, abstract, heading word, table of contents, key concepts]
7. (estrogen replacement therap$ or ert or hrt).mp. or ht.tw. [mp=title, abstract, heading word, table of contents, key concepts]
8. exp Progestational Hormones/ or exp Progesterone/
9. or/4-8
10. (endometri$ adj5 hyperplas$).tw.
11. (endometri$ adj5 (biops$ or histolog$)).tw.
12. 10 or 11
13. 3 and 9 and 12
14. 3 and 9
15. 3 and 9
16. 2007$.mp. or 2008$.up. [mp=title, abstract, heading word, table of contents, key concepts]
17. 3 and 9

Appendix 4. Cinahl search strategy

1. exp climacteric/
2. (climacteri$ or menopaus$).tw.
3. (postmenopaus$ or post-menopaus$).tw.
4. or/1-3
5. exp Contraceptives, Oral/
6. exp Estrogens/
7. Hormone Replacement Therapy/
8. exp Progestational Hormones/
9. (hormone replacement therapy or hrt).tw.
10. (estrogen$ or progest$ or oestrogen$).tw.
11. or/5-10
12. 4 and 11
13. hyperplasia/ and endometri$.tw.
14. (endometria$ adj5 hyperplas$).tw.
15. ((bleed$ or spotting) adj5 vagina$).tw.
16. (endometri$ adj5 (Carcinoma$ or cancer$)).tw.
17. (endometri$ adj5 (biops$ or histol$ or thickness$)).tw.
18. exp Uterine Hemorrhage/
19. or/13-18
20. 12 or 19
21. controlled study/ or randomized controlled trial/
22. (drug$ adj5 Compar$).tw.
23. placebo/
24. random$.tw.
25. latin square.tw.
26. (crossover or cross-over).tw.
27. placebo$.tw.
28. ((doubl$ or singl$ or Tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
29. (comparative adj5 trial$).tw.
30. (clinical adj5 trial$).tw.
31. or/21-30

32. animal/ not (human/ and animal/)
33. 31 not 32
34. 33 and 20

Appendix 5. MDSG register search strategy

((Keywords = "*Menopaus*" or Keywords = "postmenopaus*" or #43= "menopaus*" or #43="postmenopausal") and (Keywords ="*Hormone Therap*" or Keywords = "HRT*" or Keywords = "HT* ")and (Keywords = "endometrial biops*" or Keywords = "endometrial hyperpla*" or Keywords ="endometrial response*" or Keywords = "endometrial proliferat*" or Keywords ="bleeding*" or #43= "bleeding pattern*")) AND NOT (Keywords = "tibolone" or Keywords = "SERM" or Keywords ="raloxifene" or Keywords = "phytoestrogen*")

WHAT'S NEW

Last assessed as up-to-date: 8 July 2007.

Date	Event	Description
20 September 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 2, 1999

Date	Event	Description
11 February 2009	New citation required but conclusions have not changed	This review was updated July 2008
21 October 2008	New search has been performed	Review update involved an extensive overhaul of the entire orginal review
21 October 2008	Review declared as stable	The conclusion of this review are now regarded as stable
15 September 2008	Amended	Title changed as irregular bleeding no longer a focus of the review and for simplicity removed in postmenopausal women
16 July 2008	New search has been performed	Protocol amended, new search done and review updated
15 April 2008	Amended	Converted to new review format.

(*Continued*)

9 July 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the 2008 update of this review

Sue Furness modified the protocol, performed searches, selected trials for inclusion, assessed quality, performed data extraction, entered data, prepared the final review and incorporated suggested changes.

Helen Roberts modified the protocol, contributed to the design of the table of comparisons and results section of the text, and wrote the implications for practice and research sections.

Jane Marjoribanks selected trials for inclusion, assessed quality, performed data extraction and made detailed comments on many drafts of the text.

Anne Lethaby reviewed the protocol, contributed to the methods and results sections and made detailed comments on several drafts of the text.

Martha Hickey reviewed the protocol, collated the data on the endometrial effects of progestogens, and commented on the final review.

Cindy Farquhar reviewed the protocol and commented on the final draft of the review.

DECLARATIONS OF INTEREST

There was no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Dept of Obstetrics and Gynaecology, University of Auckland, New Zealand.

External sources

- Health Research Council, New Zealand.

INDEX TERMS

Medical Subject Headings (MeSH)

*Estrogen Replacement Therapy [adverse effects]; Endometrial Hyperplasia [chemically induced; *prevention & control]; Endometrial Neoplasms [chemically induced; prevention & control]; Estrogens [*administration & dosage]; Postmenopause; Progestins [*administration & dosage]; Randomized Controlled Trials as Topic; Uterine Hemorrhage [chemically induced; prevention & control]

MeSH check words

Female; Humans