Published in final edited form as:

Cochrane Database Syst Rev. ; (12): CD007926. doi:10.1002/14651858.CD007926.pub2.

Hormonal therapy in advanced or recurrent endometrial cancer

Fani Kokka¹, Elly Brockbank¹, David Oram¹, Chris Gallagher², and Andrew Bryant³

¹Department of Gynaecological Oncology, St. Bartholomew's Hospital, London, UK

²Medical Oncology, St Bartholomew's Hospital, London, UK

³Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Abstract

Background—Endometrial cancer is a cancer of the lining of the womb and worldwide is the seventh most common cancer in women. Treatment with hormones is thought to be beneficial in patients with endometrial cancer.

Objectives—To assess the indications, effectiveness and safety of hormone therapy for advanced or recurrent epithelial endometrial cancer.

Search methods—We searched the Cochrane Gynaecological Cancer Group Trials Register, MEDLINE, EMBASE up to May 2009 and and CENTRAL (Issue 2, 2009). We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies, and contacted experts in the field.

Selection criteria—Randomised controlled trials (RCTs) that studied hormonal therapy in adult women diagnosed with advanced or recurrent endometrial cancer.

Data collection and analysis—Two review authors independently abstracted data and assessed risk of bias. Comparisons were restricted to single-trial analyses so we did not synthesise data in meta-analyses.

Main results—We found six trials (542 participants) that met our inclusion criteria. These trials assessed the effectiveness of hormonal therapy in women with advanced or recurrent endometrial cancer as a single agent, as part of combination therapy and as low versus high dose.

All comparisons were restricted to single-trial analyses, where we found no evidence that hormonal therapy as a single agent or as a combination treatment prolonged overall or five-year disease-free survival of women with advanced or recurrent endometrial cancer. However, low-dose hormonal therapy may have had a benefit in terms of overall and progression-free survival

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd

Contact address: Fani Kokka, Department of Gynaecological Oncology, St. Bartholomew's Hospital, Barts and The London Trust, West Smithfield, London, EC1A 7BE, UK. fani.kokka@bartshealth.nhs.uk. fanikokka@yahoo.com.

CONTRIBUTIONS OF AUTHORS FK, EB, DO and CG drafted the clinical sections of the review; AB and HD drafted the methodological sections of the review. All authors agreed the final version.

Editorial group: Cochrane Gynaecological Cancer Group.

Publication status and date: Edited (no change to conclusions), published in Issue 3, 2014.

Review content assessed as up-to-date: 9 November 2010.

DECLARATIONS OF INTEREST None known.

(PFS) compared to high-dose hormonal therapy (HR 1.31, 95% CI 1.04 to 1.66 and HR 1.35, 95% CI 1.07 to 1.71 for overall and PFS, respectively).

Authors' conclusions—We found insufficient evidence that hormonal treatment in any form, dose or as part of combination therapy improves the survival of patients with advanced or recurrent endometrial cancer. However, a large number of patients would be needed to demonstrate an effect on survival and none of the included RCTs had a sufficient number of patients to demonstrate a significant difference. In the absence of a proven survival advantage and the heterogeneity of patient populations, the decision to use any type of hormonal therapy should be individualised and with the intent to palliate the disease. It is debatable whether outcomes such as quality of life, treatment response or palliative measures such as relieving symptoms should take preference over overall and PFS as the major objectives of future trials.

Medical Subject Headings (MeSH)

Antineoplastic Agents, Hormonal [*therapeutic use]; Disease-Free Survival; Drug Therapy, Combination [methods]; Endometrial Neoplasms [*drug therapy; mortality]; Hydroxyprogesterones [therapeutic use]; Medroxyprogesterone Acetate [therapeutic use]; Megestrol [therapeutic use]; Neoplasm Recurrence, Local [*drug therapy; pathology]; Neoplasm Staging; Progestins [*therapeutic use]

MeSH check words

Adult; Female; Humans

BACKGROUND

Description of the condition

Endometrial cancer is a cancer of the lining of the womb and worldwide is the seventh most common cancer in women (GLOBOCAN 2002). It is consistently associated with obesity (Armstrong 1975; Chang 2008; Hill 1996; Kaaks 2002; Lindemann 2008) and it is more common in developed countries: the age-standardised incidence is 13.6 per 100,000 women per year in more developed countries, compared with 3.0 per 100,000 per year in less developed countries. Endometrial cancer occurs predominately around or after the menopause (GLOBOCAN 2002). Most women are diagnosed at an early stage and are cured by surgery alone. About 10% of women with endometrial cancer are diagnosed when the disease is already at an advanced stage (FIGO stages III and IV, which is staging according to the International Federation of Gynecology and Obstetrics) and have much poorer survival (Jemal 2008). In Stage III the cancer has extended outside the uterus but not outside the true pelvis. In stage IV the cancer has extended outside the true pelvis or it has obviously involved the inner lining of the bladder or rectum. Treatment of Stage III and IV disease is individualised but usually involves a combination of surgery, radiation therapy and/or chemotherapy (Berek 2005). Recurrent endometrial cancer is cancer that has come back after it has been treated. The cancer may come back in the pelvis, in the lymph nodes, in the abdomen, or in other parts of the body. A local recurrence is usually defined as tumour regrowth anywhere in the pelvic structures or in the lymph nodes located below the pelvic brim (the uppermost edge of the pelvis). Distant metastases is disease outside the pelvis.

Confirmation of local or distant recurrences is based on biopsies, clinical examination and radiological findings (Aalders 1984). Progression of cancer is similarly diagnosed with biopsies, clinical examination and radiological findings, where a patient who is known to have remaining endometrial cancer has a larger volume of disease or distant metastases that she did not have before.

The prognosis after treatment of recurrent endometrial cancer by the current methods is poor (Aalders 1984). In general, patients with low-volume recurrence limited in the vagina have a higher possibility of local control and a better outcome than women with multiple sites of disease and liver metastases (Ackerman 1996; Sears 1994; Sohaib 2007).

Cancer is spread locally and through blood, lymphatic system and peritoneum (the layer covering the walls and organs of the abdomen). A small proportion of women with recurrent or advanced-stage endometrial cancer present with solitary metastatic lesions (single areas of disease having spread from the womb to another part of the body) that can be treated by radiation with or without surgical excision. Also radiation can be used for vaginal recurrences (Sears 1994; Temkin 2009). However, in the majority of cases, advanced or recurrent endometrial cancer is a systemic disease with multiple metastases that requires a systemic treatment with radiotherapy and/or chemotherapy (standard treatment) which may have significant side effects (Carey 2006; Santin 2004) or not always be possible due to major co-morbidities.

Description of the intervention

Treatment with hormones is thought to be useful in the management of endometrial cancer because the normal endometrial cells grow in response to hormones. In particular, the endometrial cells proliferate in response to oestrogen (one type of hormone) exposure, while this effect is arrested by progesterone (another type of hormone), as seen in the normal menstrual cycle (Decruze 2007). Endometrial cancer develops from poorly controlled endometrial proliferation that is thought to be due to genetic alterations (Levine 1998). Excessive endometrial proliferation may be driven by endogenous or exogenous overexposure to oestrogens. For example, the frequency of endometrial cancer is increased when replacement oestrogens are prescribed without progestogens (Jick 1979). Similarly, patients with overexposure to oestrogens due to conditions like obesity, polycystic ovarian syndrome (a common hormonal disorder), early menarche (first menstrual period) and late menopause (complete cessation of menses), are at higher risk of developing endometrial cancer (Hill 1996). This type of endometrial cancer is called type I and accounts for the majority of cases. They are usually well differentiated in histology (resemble normal endometrium) and the majority of them are diagnosed in early stage. Type II endometrial cancers are poorly differentiated tumours (have little macroscopic resemblance with normal endometrial tissue), which may not be associated with overexposure to oestrogens, are more likely to present in advanced stage and recur more often (Santin 2004), possibly because they tend to be more aggressive tumours. There is no difference in symptoms between the two types; both usually cause abnormal vaginal bleeding.

Response of endometrial cancer to hormonal treatment is difficult to predict. It is thought to be better when certain oestrogen (ER) or progesterone (PR) receptors (molecular structures)

have been identified in the cancer tissue, which are more common in type I endometrial cancers (Decruze 2007; Podratz 1985; Singh 2007). However, there have been reports identifying response without these features (Kauppila 1984; Lentz 1996; Obel 2006; Temkin 2009). Assessment of hormonal receptors of cancer has been recommended, especially in cases of clinical trials because this may aid clinical management with hormonal treatment in selected cases (Decruze 2007; Singh 2007). On the other hand, patients presenting with advanced or recurrent disease may respond differently from patients with early disease, because of differences in symptoms, tumour size, tumour biology and prior treatment (e.g. radiation, chemotherapy) (Sehouli 2008).

Hormonal treatment in advanced or recurrent stages of endometrial cancer is thought to be easily administered and to cause fewer side effects than systemic chemotherapy (standard treatment). This is particularly important for patients with poor performance status (a measurement of general health) and/or multiple co-morbidities that are frequently encountered in patients with endometrial cancer (Santin 2004; Sehouli 2008; Temkin 2009). Various hormonal therapies have been reported including progestins (medroxyprogesterone acetate, megestrol acetate, 17 α -hydroxyprogesterone caproate, 6, 17 α -dimethyl-6-dehydroprogesterone, 6-methyl-6-dehydroprogesterone acetate), selective estrogen receptor modulators (SERMs, e.g. tamoxifen, arzoxifene), aromatase inhibitors (anastrozole, letrozole), synthetic steroid derivative (danazol), gonadotropin-releasing hormone (GN-RH) analogues or combination of the above or combination of hormonal with chemotherapeutic agents (Asbury 2002; Covens 1997; Covens 2003; Decruze 2007; Fiorica 2004; Gallagher 1991; Jeyarajah 1996; Kauppila 1984; Ma 2004; Markman 1997; Piver 1980; Podratz 1985; Quinn 1989; Rose 2000; Whitney 2004). In advanced cases of endometrial cancer, hormonal treatment has been used in order to relieve the symptoms of the disease (most commonly excessive vaginal bleeding) and if possible to prevent progression. A review of systemic progestin therapy showed objective remission in about one-third of patients treated in 17 studies (Kauppila 1984). However, it is not specified in detail what studies were included and whether the included studies had comparison groups. Other studies have shown overall responses with hormonal agents ranging from 9% to 55% (Asbury 2002; Lentz 1996; Ma 2004; Piver 1980; Podratz 1985; Rose 2000; Thigpen 2001; Whitney 2004).

There is conflicting evidence regarding the effective dose of progesterone therapy in advanced or recurrent endometrial cancer and the route of administration seems to be of minor importance (Kauppila 1984), but this has not been addressed in a systematic review. According to some authors, high-dose progesterone therapy does not appear to have any additional benefit in survival or response (Lentz 1996; Moore 1991; Santin 2004; Thigpen 1999) and some reviews have even shown better overall survival and response in patients receiving a lower dose (Carey 2006).

The most common toxicity of progestogens and SERMs appears to be thrombosis (development of clots in the vessels) (Burke 2003; Fiorica 2004; Lentz 1996; Markman 2004).

Why it is important to do this review

Survival of patients with endometrial cancer has not improved substantially over the past 25 years and although most cases are detected and treated in early stages, a significant number of women present at advanced stage (Jemal 2008). Often these patients suffer from major co-morbidities (Kitchener 2008) and consequently, aggressive chemotherapy and/or surgery may not be beneficial or may even be harmful.

Phase II studies have demonstrated a high response rate in some of the hormonal agents (McMeekin 2003; Whitney 2004) and considering their favourable toxicity profile, they could be extremely useful for patients with advanced or recurrent endometrial cancer. Kauppila et al completed a review of progestin therapy of endometrial, breast and ovarian carcinoma (Kauppila 1984). However, it was not a systematic review and details of the type of studies included were not stated. Also, it was carried out more than 20 years ago and additional experience from studies that followed could lead to new recommendations regarding hormonal treatment in advanced or recurrent endometrial cancer.

Martin-Hirsch et al have completed a Cochrane Review of adjuvant therapy after primary surgery for endometrial cancer (Martin-Hirsch 1999). However, women with inoperable or advanced endometrial cancer or with major co-morbidities, form a subgroup of patients that needs to be reviewed separately in view of different tumour response to treatment, management options and possibly different treatment objectives, compared to patients with early disease.

OBJECTIVES

To assess the indications, effectiveness and safety of hormone therapy for advanced or recurrent epithelial endometrial cancer.

METHODS

Criteria for considering studies for this review

Types of studies—

- Randomised controlled trials (RCTs).

Types of participants—Women with a confirmed histological diagnosis of advanced (FIGO stage III or IV) or recurrent endometrial cancer.

We excluded trials accruing women who had uterine carcinosarcoma or sarcoma because these types of cancer behave differently from the common endometrial cancer.

Types of interventions

Intervention: Hormonal treatment:

- Progestins (medroxyprogesterone acetate, megestrol acetate, 17a-hydroxyprogesterone caproate, 6, 17a-dimethyl-6-dehydroprogesterone, 6-methyl-6-dehydroprogesterone acetate)

- Selective oestrogen receptor modulators (tamoxifen, arzoxifene)
- Aromatase inhibitors (anastrozole, letrozole)
- Synthetic steroid derivative (danazol)
- GN-RH analogues
- Combination of the above or combination of hormonal with chemotherapeutic agents

Comparison:

- Alternative treatment:
 - Combination chemotherapy-double agents (cisplatin, doxorubicin)
 - Combination chemotherapy-triple agents (paclitaxel, cisplatin, doxorubicin)
 - Combination chemotherapy with hormonal treatment
 - Radiotherapy with or without chemotherapy
- Best supportive care

Additionally, we considered any direct comparisons between different types and doses of hormonal treatments.

Types of outcome measures

Primary outcomes:

1. Overall survival (OS): survival until death from all causes. Survival was assessed from the time when women were enrolled in the study.

Secondary outcomes:

1. Progression-free survival (PFS)
2. Quality of life (QoL) measured using a scale that had been validated through reporting of norms in a peer-reviewed publication
3. Adverse events classified according to Common Terminology Criteria for Adverse Events (CTCAE 2006):
 - i) haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage)
 - ii) gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis)
 - iii) genitourinary
 - iv) skin (stomatitis, mucositis, alopecia, allergy)
 - v) neurological (peripheral and central)
 - vi) menopausal symptoms (e.g. hot flushes)
 - vii) other (e.g. weight gain)

Search methods for identification of studies

We sought papers in all languages and carried out translations if necessary.

Electronic searches—See: Cochrane Gynaecological Cancer Group methods used in reviews.

We searched the following electronic databases:

- the Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2009);
- MEDLINE
- EMBASE

The MEDLINE, EMBASE and CENTRAL search strategies aiming to identify RCTs comparing hormonal therapy in advanced or recurrent endometrial cancer before May 2009 are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.

We searched databases from the first published report of hormonal treatment in endometrial cancer (Kelley 1965) until May 2009. All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

Unpublished and grey literature: We searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (<http://www.g-o-c.org>) for ongoing trials. We contacted the main investigators of one ongoing trial (Bloss) for further information, and major co-operative trials groups active in this area.

Handsearching: We handsearched reports of conferences in the following sources:

- *British Journal of Cancer*;
- British Cancer Research Meeting;
- Annual Meeting of the British Gynaecological Cancer Society;
- Annual Meeting of the International Gynecologic Cancer Society;
- Annual Meeting of the American Society of Gynecologic Oncologists;
- Annual Meeting of European Society of Medical Oncology (ESMO);
- Annual Meeting of the American Society of Clinical Oncology (ASCO);
- Annual Meeting of the National Cancer Research Institute (NCRI); and
- Annual Meeting of the European Society of Gynaecological Oncology (ESGO).

Reference lists and correspondence: We checked the citation lists of included studies and contacted experts in the field to identify further reports of trials. We contacted pharmaceutical companies that manufacture hormonal treatments used in advanced or recurrent endometrial cancer and these included Bristol-Myers Squibb Pharmaceuticals Limited for megestrol acetate, Pfizer for medroxyprogesterone acetate and Astra Zeneca for tamoxifen (TMX).

Data collection and analysis

Selection of studies—We downloaded all titles and abstracts retrieved by electronic searching to the reference management database Endnote and duplicates. The remaining references were examined by two review authors (FK, EB) independently. We excluded those studies which clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (FK, EB) independently assessed the eligibility of retrieved papers. Disagreements were resolved by discussion between the two review authors and when necessary by a third review author (DHO or CG). Reasons for exclusion are documented (Characteristics of excluded studies).

Data extraction and management—For included studies, we abstracted data as recommended in chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This included data on the following.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
 - total number enrolled
 - patient characteristics
 - age
 - co-morbidities
 - previous treatment
 - performance status
- Endometrial cancer details at diagnosis
 - FIGO stage
 - histological cell type
 - tumour grade
 - extent of disease

- recurrent disease
- Total number of intervention groups
- Hormonal therapy details
 - type e.g. progestins (medroxyprogesterone acetate, megestrol acetate, 17 α -hydroxyprogesterone caproate, 6,17 α -dimethyl-6-dehydroprogesterone, 6-methyl-6-dehydroprogesterone acetate), selective oestrogen receptor modulators (tamoxifen, arzoxifene), aromatase inhibitors (anastrozole, letrozole), danazol (synthetic steroid derivative), Gn-RH analogues
 - dose
 - duration
 - combination of above (or combination of hormonal with chemotherapeutic agents)
- Comparison details
 - alternative treatment, e.g. chemotherapy
 - ◇ dose (if appropriate)
 - ◇ duration (if appropriate)
 - ◇ combination (e.g. chemotherapy with hormonal treatment, radiation with hormonal treatment)
 - best supportive care
- Risk of bias in study (see below)
- Duration of follow up
- Outcomes: OS, PFS, QoL and adverse events:
 - for each outcome: outcome definition;
 - unit of measurement (if relevant);
 - for scales: upper and lower limits, and whether high or low score is good
 - results: number of participants allocated to each intervention group;
 - for each outcome of interest: sample size; missing participants.

We extracted data on outcomes as below:

- For time to event (OS) data, we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events or deaths if it was not possible to use a HR), we extracted the number of patients in each group who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).

We extracted both unadjusted and adjusted statistics, if reported. Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in groups to which they were assigned.

We noted the time points at which outcomes were collected and reported.

Two review authors (FK, EB) abstracted data independently onto a data abstraction form specially designed for the review. Differences between review authors were resolved by discussion or by appeal to a third review author (AB, DHO or CG) when necessary.

Assessment of risk of bias in included studies—We assessed the risk of bias in the included RCTs using the Cochrane Collaboration's tool and the criteria specified in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data:
 - We coded the satisfactory level of loss to follow up for each outcome as:
 - ◇ Yes, if fewer than 20% of patients were lost to follow up and reasons for loss to follow up were similar in both treatment arms;
 - ◇ No, if more than 20% of patients were lost to follow up or reasons for loss to follow up differed between treatment arms;
 - ◇ Unclear, if loss to follow up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (FK, EB) applied the risk of bias tool independently and resolved differences by discussion or by appeal to a third review author (AB, DHO or CG). Results are summarised in both a 'Risk of bias' graph and a 'Risk of bias' summary. We interpreted results of meta-analyses in light of the findings with respect to risk of bias.

Measures of treatment effect—We used the following measures of the effect of treatment:

- For time to event data, we used the hazard ratio (HR), where possible.
- For dichotomous outcomes, we used the risk ratio (RR).

Dealing with missing data—We did not impute missing outcome data; if only imputed outcome data were reported, we contacted trial authors to request data on the outcomes only among participants who were assessed.

Data synthesis—The review was restricted to single-trial analyses so it was not possible to perform meta-analyses. Therefore it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup analyses or sensitivity analyses.

RESULTS

Description of studies

Results of the search—The search strategy identified 809 unique references. Three authors read the abstracts of these independently and excluded articles which obviously did not meet the inclusion criteria at this stage. We retrieved 26 articles in full, translated these into English where appropriate and identified updated versions of relevant studies. The full text screening of these 26 references excluded 20 of them for the reasons described in the table Characteristics of excluded studies. However, six completed RCTs were identified that met our inclusion criteria and are described in the table Characteristics of included studies.

Searches of the grey literature identified one additional ongoing trial (Bloss).

Included studies—The six included trials (Ayoub 1988; Pandya 2001; Rendina 1984; Stolyarova 2001; Thigpen 1999; Urbanski 1993) randomised 542 eligible women, of whom 539 were assessed for survival outcomes and 536 for adverse events at the end of the trials.

In all studies, the patients received progestins (medroxyprogesterone acetate, hydroxyprogesterone caproate, megestrol, 17-oxyprogesterone caproate) in various forms and combinations with other drugs or treatment modalities. In three trials the patients had advanced or recurrent disease (Pandya 2001; Rendina 1984; Thigpen 1999) and in the other three all stages were included, but we analysed the results for the those with advanced or recurrent endometrial cancer (Ayoub 1988; Stolyarova 2001; Urbanski 1993).

The review identified the following treatment comparisons for the six included studies:

- single-agent hormonal treatment versus different single-agent hormonal treatment;
- chemotherapy versus chemo-hormonal therapy;
- single-agent adjuvant hormonal treatment versus no adjuvant hormonal treatment;
- single-agent hormonal treatment versus double-agent hormonal treatment;
- single low-dose hormonal treatment versus single high-dose hormonal treatment;
- single-agent hormonal treatment and radiotherapy versus radiotherapy only.

The duration of follow up of patients varied from 24 months to 60 months.

Trial comparing different single agents of hormonal treatment: The Rendina 1984 trial was a balanced prognostic study of one cancer centre in Italy. A group of 93 patients with stage III or IV endometrial adenocarcinoma were randomly allocated to therapy for four months with tamoxifen (TMX) 20 mg twice daily or medroxyprogesterone acetate (MPA) 1 g/wk intramuscularly. Those patients unresponsive after the first four months of treatment

with a single therapy were given a combination of TMX and MPA and again examined every four months. They assessed the one-year survival and the side effects. Side effects were reported by treatment arm, but their categorisation was different and therefore not directly comparable.

Trial comparing chemotherapy versus chemo-hormonal therapy: The trial of Ayoub 1988 was a multi-centre stratified randomised controlled trial from Canada. A subset of 43 patients with stage IV and recurrent endometrial cancer from total study population of 262 patients were randomised to chemotherapy (CAF: cyclophosphamide, adriamycin, 5-fluorouracil) or to chemo-hormonal therapy (CAF and MPA and TMX). They assessed the overall survival, the objective tumour response and the duration of remission. The median age of the patients was 63 years. Their performance score was 2. Randomisation was stratified by the site of advanced disease (pelviabdominal versus distant metastases). The treatment groups were well balanced with respect to whether the disease was newly diagnosed (i.e. *de novo* Stage IV disease) or recurrent, and with respect to whether patients had received palliative radiation or not, prior to commencing chemo- or chemo-hormonal therapy. The exact log rank P value from the Kaplan Meier plot was not reported so it was not possible to estimate the hazard ratio (Parmar 1998). We deduced death within two years from the Kaplan Meier plot and the number of reported deaths in each group.

Trial comparing single-agent adjuvant hormonal treatment versus no adjuvant hormonal treatment: The trial of Urbanski 1993 is a multi-centre randomised controlled trial from Poland. A group of 205 patients with endometrial cancer stage I-III entered the study and were randomised to hydroxyprogesterone caproate or not. The median age of the patients was 56 years with a range of 4 to 80 years. In more than half of the patients histological diagnosis did not define histological grade. Histological type and grade were not given by stage. Data were available for a subset of 31 women who had stage III endometrial cancer. Patients with poor prognostic factors were treated postoperatively with external pelvic irradiation and/or intracavitary radium, however we do not know how many of those had stage III disease. Patients were assessed for overall survival, endometrial cancer-related deaths, cancer-related deaths and disease relapse. The duration of follow up in the trial was 60 months. The exact log rank P value from the Kaplan Meier plot was not reported so it was not possible to estimate the hazard ratio (Parmar 1998). The overall five-year survival rate by stage and treatment group was reported.

Trial comparing different dosing of the same agent hormonal treatment: The Thigpen 1999 trial was a multi-centre randomised controlled trial from USA. The aim was to determine whether an increased dose of oral progestin could improve the observed response rate in endometrial carcinoma. A group of 299 patients with advanced or recurrent endometrial adenocarcinoma and not amenable to control with surgery and/or radiotherapy were randomly allocated to therapy of low-dose (200 mg/d) MPA or high-dose (1000 mg/d) MPA. They assessed the overall survival, the response, the progression-free survival and the serum level of MPA. The latter was also used in order to assess patient compliance to oral treatment. There were no appreciable differences between the patients on the two regimens with regard to age, performance status, prior treatment with surgery and/or radiotherapy,

stage, cell type, or histological grade. In addition, for the 132 patients who had data available for both oestrogen and progesterone receptors there were no appreciable differences observed between the two regimens with regard to receptor status. From the Kaplan Meier plot the duration of follow up ranged from 0 to 48 months. Adjusted hazard ratios using Cox regression for overall and progression-free survival were reported. The Cox model was adjusted for the initial performance status, progesterone-receptor level, tumour grade and age. Thrombophlebitis was reported by treatment arm.

Trial comparing single-agent hormonal therapy versus double-agent hormonal

therapy: The trial of Pandya 2001 was a multi-centre randomised controlled trial from the USA. A group of 62 patients with advanced endometrial cancer were randomly allocated to therapy with megestrol or megestrol and TMX. Twenty patients with advanced endometrial cancer were randomised to the megestrol group and 42 to the megestrol and tamoxifen group. The median age in the megestrol arm was 68 years. The median age in the megestrol and tamoxifen arm was 65 years. Sixteen (26%) patients were less than 60 years of age, 26 patients (42%) were 61 to 70 years of age and 20 (32%) were over 70 years of age. Thirty-two (52%) women had Grade 1 and 2 disease, 29 (47%) had Grade 3 disease and Grade was unknown in one patient (2%). Twenty-two (35%) women had performance status 'fully active', 29 (47%) had status 'ambulatory' and 11 (18%) had status 'in bed 50%'. Overall survival and response were assessed. The megestrol arm was terminated early because of poor accrual. There was no imbalance at baseline between the two groups. The exact log rank P value from the Kaplan Meier plot was not reported so it was not possible to estimate the hazard ratio (Parmar 1998). We deduced death within five years from the Kaplan Meier plot and the number of reported deaths in each group.

Trial comparing single-agent hormonal therapy and radiotherapy versus radiotherapy

only: The trial of Stolyarova 2001 is a single-centre randomised controlled trial from Russia. Seventy-six patients with endometrial adenocarcinoma not amenable to surgery because of medical reasons or advanced stage entered into the study. Data were available for a subgroup of 14 patients with stage III disease that were randomly allocated to radiotherapy (RT) and 17-oxyprogesterone caproate (OPC) or radiotherapy only. Most of the patients were given RT in the form of external beam irradiation alternating with intracavitary high-dose rate (HDR) brachytherapy, while some of them received only intracavitary HDR brachytherapy due to obesity. The duration of follow up was not reported. The impact of hormonal therapy on five-year disease-free survival (DFS) was studied. Tumour differentiation and type of RT were given for all the included patients, but not by stage.

Excluded studies—We excluded 20 references, after obtaining the full text, for the following reasons:

- Six references (Carey 2006; Decruze 2007; Humber 2005; Martin-Hirsch 1996; Martin-Hirsch 1999; Polyzos 2006) were systematic reviews that yielded no further included trials. Polyzos 2006 found a possible trial (Piver 1986). This was afterwards excluded because the trial randomised a subset of 18 patients, but was later discontinued and did not report any of the outcomes specified in our review for the randomised patients.

- Six trials (Behling 1983; Deng 2000; Krafft 1990; Macdonald 1988; Vavra 1990; Vishnevsky 1993) did not report by treatment and stage so it was not possible to distinguish between early and late-stage disease.
- One cross-over trial (Bruera 1998) was excluded as the primary outcomes in this review were overall and progression-free survival. Quality of life was an outcome in the trial, but was not reported by treatment group and cancer type.
- In one trial (Cohen 1984) it was unclear which patients were randomised.
- Three references (Kneale 1988; Lentz 1996; Piver 1980) were not RCTs. Lentz 1996 and Piver 1980 were nonrandomised studies and Kneale 1988 was a letter to the authors of the trial of Macdonald 1988.
- In the trial of COSA trial, the authors could not provide us with data that we could include in the review.
- One trial (Lotze 1982) randomised 10 women to receive hormonal therapy, but the trial had many weaknesses. The main weakness was the reporting of survival data, where deaths were checked at yearly intervals and length of follow up differed between the different groups so calculating a risk ratio was not possible.
- The trial of Zhang 1996 did not report any of the outcomes specified in this review.

For further details of all the excluded studies see the table Characteristics of excluded studies.

Risk of bias in included studies

Four trials (Ayoub 1988; Pandya 2001; Rendina 1984; Thigpen 1999) were at moderate risk of bias: they satisfied three of the criteria that we used to assess risk of bias. The trials of Stolyarova 2001 and Urbanski 1993 were at high risk of bias as they only satisfied one criterion (see Figure 1; Figure 2).

Three trials (Ayoub 1988; Rendina 1984; Thigpen 1999) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms, but two of these trials (Ayoub 1988; Thigpen 1999) did not report concealment of this allocation sequence from patients and healthcare professionals involved in the trial and Rendina 1984 did not attempt to conceal the allocation. Two trials (Stolyarova 2001; Urbanski 1993) did not report on either the method of sequence generation or concealment of allocation. In the trial of Pandya 2001 it was unclear whether the method of assigning women to treatment groups was carried out using an adequate method of sequence generation, but the allocation was adequately concealed. None of the trials reported whether the patients, healthcare professionals or outcome assessors were blinded. Four trials (Pandya 2001; Rendina 1984; Thigpen 1999) accurately classified outcomes, but this was unclear in the trials of Stolyarova 2001 and Urbanski 1993. It was not certain whether all trials reported all the outcomes that they assessed and it was unclear whether any other bias may have been present. At least 93% of women who were enrolled were assessed at endpoint in all six trials.

Effects of interventions

MPA versus tamoxifen

Death within one year: (see Analysis 1.1)

The trial of Rendina 1984 found no statistically significant difference in the risk of death in women who received MPA and tamoxifen (RR 1.00, 95% CI 0.77 to 1.29). Those patients unresponsive after the first “four months” treatment with a single therapy were given a combination of TMX and MPA and again examined every four months. By the end of the trial all patients were receiving combination therapy, which may explain the similarity in survival between the two groups. No severe adverse effect was reported in either treatment group.

CAF and MPA followed by tamoxifen versus CAF alone

Death within two years: (see Analysis 2.1)

The trial of Ayoub 1988 found no statistically significant difference in the risk of death in women who received chemo-hormonal therapy and chemotherapy alone (RR 0.80, 95% CI 0.48 to 1.33).

Adjuvant progestagen therapy versus control

Death within five years: (see Analysis 3.1)

The trial of Urbanski 1993 found no statistically significant difference in the risk of death in women with advanced endometrial cancer who received adjuvant progestagen therapy and those who received no adjuvant progestagen therapy (RR 0.08, 95% CI 0.01 to 1.28).

High-dose MPA versus low-dose MPA

Overall survival: (see Analysis 4.1)

The trial of Thigpen 1999 found that women who received high-dose MPA for treatment of advanced or recurrent endometrial cancer had a significantly higher risk of death than women who received low-dose MPA, after adjustment for performance status, progesterone-receptor level, tumour grade and age (HR 1.31, 95% CI 1.04 to 1.66).

Progression-free survival: (see Analysis 4.2)

The trial of Thigpen 1999 found that women who received high-dose MPA for treatment of advanced or recurrent endometrial cancer had a significantly higher risk of disease progression than women who received low-dose MPA, after adjustment for initial performance status, progesterone-receptor level, tumour grade and age (HR 1.35, 95% CI 1.07 to 1.71).

Thrombophlebitis: (see Analysis 4.3)

In the trial of Thigpen 1999, adverse events were not common with either of the two regimens, and no differences in toxicity were noted between the two arms of the study (data

not provided). For the most commonly reported adverse event, there was no statistically significant difference in the risk of thrombophlebitis in women who received high-dose and low-dose MPA (RR 1.24, 95% CI 0.43 to 3.60). No other severe adverse events were reported.

Megestrol and tamoxifen versus megestrol

Death within five years: (see Analysis 5.1)

The trial of Pandya 2001 found no statistically significant difference in the risk of death in women who received a combination of megestrol and tamoxifen and those who received megestrol alone (RR 1.03, 95% CI 0.87 to 1.22). Initial performance status is the only covariate that retained significance in the stepwise proportional hazards regression of survival.

Adverse events: The megestrol-only arm induced mild and moderate side effects. Severe to life-threatening toxicities, one of them being pulmonary embolism, were seen in only two women in the trial. Both women received combination therapy, but this was not statistically significant.

OPC and radiotherapy versus radiotherapy alone

Five-year disease-free survival: (see Analysis 6.1)

The trial of Stolyarova 2001 found no statistically significant difference in the risk of death in women with advanced disease who received hormonal-radiation therapy and radiotherapy alone (RR 1.00, 95% CI 0.40 to 2.48).

DISCUSSION

Summary of main results

We found six trials that met our inclusion criteria. These trials assessed the effectiveness of hormonal therapy as either a single agent, part of combination therapy or examined low versus high-dose hormonal therapy in women with advanced or recurrent endometrial cancer. None of these trials compared hormonal therapy against best supportive care.

All comparisons were restricted to single-trial analyses, where we found no evidence that hormonal therapy as a single agent or as a combination treatment prolonged the survival of women with advanced or recurrent endometrial cancer. We also found no evidence that five-year disease-free survival was significantly longer for hormonal therapy in combination with radiotherapy and radiotherapy alone (RR 1.00, 95% CI 0.40 to 2.48). However, this review did find evidence that low-dose hormonal therapy had a benefit in terms of overall and progression-free survival compared to high-dose hormonal therapy (HR 1.31, 95% CI 1.04 to 1.66 and HR 1.35, 95% CI 1.07 to 1.71 for overall and progression-free survival, respectively). There was no significant difference in the number of women who had thrombophlebitis as a side effect to treatment in either the low or high-dose regimens (RR 1.24, 95% CI 0.43 to 3.60).

The trials had many weaknesses. They did not report hazard ratios which correctly allow for censoring and they did not provide information about adverse events, with the trial of Thigpen 1999 being the only exception, but this trial compared low and high dose and did not examine the effectiveness of hormonal therapy with another form of treatment. Most trials included a satisfactory number of participants and a reasonably large number of events were observed for overall survival, although the trial of Stolyarova 2001 only included 14 women with advanced stage disease. Overall there is a need for a large RCT to be carried out that specifically recruits women with advanced or recurrent endometrial cancer and reports overall and progression-free survival as well as QoL and adverse events. Any variations in dosage should also be clearly reported and subgroup analyses carried out if necessary.

Overall completeness and applicability of evidence

We did not find any trials that reported a hazard ratio for overall or progression-free survival for comparisons of hormonal therapy and other forms of treatment or variations in hormonal therapy. A hazard ratio would have correctly accounted for censoring and allowed estimates to take into account all points in time, rather than the risk ratio which may have been very different at different time points.

Although we specified quality of life as an outcome of interest, none of the trials reported this. Quality of life after treatment for cancer is an extremely important outcome, as treatment-related morbidity very often degrades the quality of the time that patients live in the future.

Hormonal treatment for advanced or recurrent endometrial cancer varies between different hospitals, and from this review there is no clear evidence to suggest whether a particular form of hormonal therapy, or indeed hormonal treatment at all, has a role in the management of advanced stages of the disease.

Quality of the evidence

We reviewed six trials assessing 542 participants that evaluated hormonal therapy in women with advanced or recurrent endometrial cancer. Loss to follow up was low. The number of women in the trials ranged considerably, with the three trials (Ayoub 1988; Stolyarova 2001; Urbanski 1993) that included a subset of advanced or recurrent cases being significantly smaller than the three trials that only included advanced stage patients. Progression-free survival, adverse events and quality of life of participants were inadequately documented. The review was restricted to single-trial analyses as all trials were heterogeneous in terms of their comparisons. Therefore, from the six included trials, we cannot reach any definitive conclusions about the effectiveness and safety of hormonal treatment. Overall survival may not be the most important endpoint in advanced disease as the death rates in all trials were reasonably high, with the exception of women in the progestagen arm in the trial of Urbanski 1993. Quality of life may be of greater importance, but this was not reported in any of the trials. There appeared to be an advantage in terms of overall and progression-free survival in one large trial for women who received low-dose

hormonal treatment. The robustness of this finding could be further examined if future trials are conducted which provide evidence on the efficacy of hormonal treatment.

None of the trials were at a low risk of bias. The authors of all the trials examining the survival benefit of women receiving hormonal treatment did not report a hazard ratio which is the best statistic to summarise the difference in risk in two treatment groups over the duration of a study when there is 'censoring', i.e. the time to death is unknown for some women as they were still alive at the end of the trial. However, the major concern was the failure to report either progression or recurrence-free survival as this information was likely to have been available to the trialists.

To test the robustness of the conclusions of the single trials more data are needed for each of the treatment comparisons to ensure higher quality evidence and to increase the precision of our estimates.

Potential biases in the review process

A comprehensive search was performed, including a thorough search of the grey literature and all studies were sifted and data extracted by at least two review authors independently. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias, i.e. studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as all the treatment comparisons were restricted to single-trial analyses.

We included trials of women with all stages of disease and analysed the subgroups of advanced/recurrent endometrial cancer cases. There is a possibility that patient characteristics in these trials may be heterogeneous compared to trials including only patients with advanced/recurrent disease, although you would expect the randomisation process to put patients with similar baseline demographics in each group.

Performance status details are mentioned in only three of the trials (Ayoub 1988; Pandya 2001; Thigpen 1999). Since a subset of patients were taken from three of the six included trials, it was possible that despite the fact that patients were initially randomised, there was a risk of imbalance for performance status between groups at baseline, due to relatively small numbers of included women. This is more of a concern because there are only single-trial analyses and these form the entire evidence base for the review. In general, it appears that good performance status has a positive effect on survival. It is not clear what impact performance status had in each treatment arm.

Agreements and disagreements with other studies or reviews

This systematic review of the currently available published trials found no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival. There were no data on progression-free survival, quality of life and adverse events were incompletely reported and were largely not reported by treatment arm.

It is noteworthy that because stages III and IV are rare and limit the undertaking of a prospective trial, most prospective trials enrol patients with advanced and recurrent disease together, when in fact these are different patient populations. They are heterogeneous in symptoms, tumour burden, tumour biology and prior treatment (e.g. radiation and chemotherapy) and this may influence any later interpretation of these trials (Carey 2006; Sehouli 2008). Thus, inclusion of all advanced-stage and recurrent endometrial cancers could dilute the effect of progestagens in more severe cases. This is one of the main reasons we excluded RCTs that included all stages together and did not report outcomes by treatment and stage in this review (Behling 1983; Bruera 1998; Deng 2000; Krafft 1990; Macdonald 1988; Vavra 1990; Vishnevsky 1993). Therefore, the above evidence cannot be said to be conclusive because there is significant heterogeneity in these trials regarding stage of disease, prior treatment, and tumour characteristics (histology, grading, presence or absence of hormonal receptors, tumour burden and biology). In particular, histological grade, presence or absence of ER/PR receptors, timing of recurrence since the original therapy, and site/size/number of metastases are some of the tumour characteristics that may or may not affect tumour response to hormonal therapy and perhaps the overall survival (COSA trial; Deng 2000; Fiorica 2004; Geisler 1973; Jeyarajah 1996; Kauppila 1984; Kohorn 1976; Lentz 1996; Ma 2004; McMeekin 2003; Piver 1980; Podratz 1985; Rendina 1984; Singh 2007; Thigpen 1999). In the trial of Thigpen 1999, those patients with grade 1 tumours exhibited the longest survival (median 18.8 months). This was significantly longer than the survival of those with grade 2 or 3 disease (median 7.5 months and 6.9 months respectively). However, the association of tumour grade and survival was not reported by treatment arm. They also demonstrated a strong relationship between higher concentrations of receptors and survival. But, again this was not reported by treatment arm. In addition, they found a marked association between receptor status and tumour grade; patients with more differentiated tumours, on average, also had higher concentrations of ER/PR receptors.

In the trial of Stolyarova 2001, univariate analyses suggested that women with low-grade and early-stage disease receiving hormonal therapy had better five-year disease-free survival compared to women not receiving hormonal therapy. This was not robust for high-grade and FIGO stage III disease in univariate analysis. Consequently, we did not find any evidence to support the use of hormonal therapy in patients with advanced-stage disease or patients with poorly differentiated tumours.

Considering the above, it is difficult to assess the direct impact of hormonal therapy on survival in advanced or recurrent endometrial cancer, because we do not know if patients live longer due to a response on treatment, or if responses occur in patients who may have superior survival due to better prognostic factors, i.e. lower tumour grade and presence of ER/PR receptors.

Progesterone has been associated with significantly increased risk of venous thromboembolism (Farquhar 2009). An earlier Cochrane Review on adjuvant progestagen therapy after primary surgery in endometrial cancer reported non-cancer deaths from progesterone, but due to heterogeneity in terms of the length of follow up the evidence was inconclusive. In addition, these outcomes were assessed as RRs rather than HRs and for cardiovascular deaths conclusions were not robust to different snapshots in time (Martin-

Hirsch 1999). If the risk of harm of progesterone is important then it should be used cautiously, but evidence is weak. Although response to hormonal treatment is commonly assessed in various studies, we have not included it as an outcome measure in our review and we focused mainly on survival outcomes. One of the reasons is that the definition of response differs due to arbitrary cut-offs and is likely to be much more heterogeneous between trials than other measures like progression-free survival. In addition, if responders are more common in one group and they live longer, then this is a consequence of the treatment being more effective and we would observe the difference in survival rather than response. Because response is an intermediate outcome, several regimens may show more promise than they do for survival. Finally, response is not too important if it does not have a benefit on survival. It may lead to symptomatic benefit, but because such gains may be offset by treatment-related toxicity, quality of life should be assessed in trials of palliative therapy with reproducible scoring systems. Quality of life data were not reported in any of the included RCTs in this review.

Tamoxifen - other hormones—The modest response rates achieved with progestins in advanced or recurrent endometrial cancer have made investigators study other drugs that exert their effect via alternative hormonally mediated mechanisms. TMX has been studied either alone or in combination with other hormones and in various doses (Bonte 1981; Carlson 1984; Edmonson 1986; Hald 1983; Quinn 1989; Slavik 1984; Swenerton 1979; Thigpen 2001; Vavra 1990; Vishnevsky 1993; Whitney 2004; Zhang 1996). Non-RCTs have supported the benefit in overall and progression-free survival in patients with advanced or recurrent endometrial cancer treated with a combination of TMX and progestins (Fiorica 2004; Vishnevsky 1993; Whitney 2004). TMX is thought to be beneficial in women with well-differentiated tumours or those with endometrial tumours that responded previously to progestins (Moore 1991; Thigpen 2001). The rationale for this regimen is that oestrogenic compounds in the endometrium, such as TMX, have been shown to increase progesterone receptors in human endometrial cancers and, therefore, could theoretically increase the effectiveness of progestins in the treatment of endometrial cancer. However, our analysis of the trial of Pandya 2001 found no statistically significant difference in overall survival from the use of combined megestrol and TMX. In this trial, 50% of the megestrol group and 45% of the combined megestrol and TMX group had poorly differentiated tumours. Rendina 1984 randomised patients to single treatments of MPA and TMX, but following this intervention, they treated non-responders and relapsed patients with a combination therapy of MPA and TMX. The authors have found a beneficial effect of combination treatment, however this was given post-hoc and only the single treatments were randomised (MPA versus TMX).

Other hormonal agents that have been explored for their role in the management of patients with advanced or recurrent endometrial cancer are aromatase inhibitors (anastrozole, letrozole), danazol and GnRH analogues but their benefit has not been clearly demonstrated (Covens 1997; Covens 2003; Jeyarajah 1996; Ma 2004; Markman 1997; Rose 2000).

Chemotherapy and hormonal treatment—Combination therapy of chemo-hormonal treatment has been investigated in non-RCTs without showing any clear benefit in the

treatment of advanced or recurrent endometrial cancer (Hoffman 1989; Lovecchio 1984). Similarly, the RCT by Ayoub 1988 did not find any statistically significant benefit of chemo-hormonal therapy compared to chemotherapy. Both arms had the same type of chemotherapy therefore it would be possible to distinguish the individual contribution of the hormonal component if there was any. Furthermore, giving a hormone with a cytotoxic agent negates one of the major advantages of hormonal treatment, i.e. elimination of the side effects associated with chemotherapy.

Side effects—Adverse events were not reported by treatment arm in any of the trials that compared different forms or combinations of hormonal therapy. The trial of Thigpen 1999 that compared high and low-dose hormonal therapy reported the rate of thrombophlebitis in each group and showed no statistically significant difference between the two groups due to few women experiencing the event.

Route of administration—Hormonal therapy in the included trials has been used orally and with intramuscular injections. The available results and review of the literature do not conclude whether either of these routes are better than the other (Kauppila 1984; Sall 1979).

Duration of hormonal treatment—Older non-RCTs have suggested that longer duration of hormonal treatment in endometrial cancer is associated with a better outcome (Podratz 1985; Reifenstein 1974; Vishnevsky 1993). The included trials in our review were significantly heterogeneous regarding this parameter. Duration ranged from two months to an indefinite period. There was insufficient evidence regarding the effect of the duration of hormonal treatment in patients with advanced or recurrent endometrial cancer.

Timing of recurrence since the original therapy—Some evidence suggests that hormonal therapy is more beneficial when there is a longer period from the initial treatment and the appearance of recurrence (Podratz 1985; Reifenstein 1974). The included RCTs in this review provide insufficient evidence to make such inferences.

AUTHORS' CONCLUSIONS

Implications for practice

From the available RCTs, we found insufficient evidence that hormonal treatment in any form, dose or as part of combination therapy improves the survival of patients with advanced or recurrent endometrial cancer. However, a large number of patients would be needed to demonstrate an effect on survival in a RCT and none of the included trials in this review had a sufficient number of patients to demonstrate a significant difference. In view of the absence of a proven survival advantage and the heterogeneity of patient populations, the decision to use any type of hormonal therapy should be individualised and with the intent to palliate the disease. It is debatable whether outcomes such as quality of life, treatment response or palliative measures such as relieving symptoms should take preference over overall and progression-free survival as the major objectives of future trials.

Implications for research

More good quality RCTs are required to assess the use of hormonal therapy in advanced or recurrent endometrial cancer. In view of the favourable toxicity profile and the ease of administration of hormonal therapy, its use should be further evaluated in these patients.

Advanced and recurrent endometrial cancer are relatively uncommon diseases, therefore multi-centre RCTs should be set up so that sufficient numbers of patients are recruited to power the trials adequately. There is a need to identify the subset of women most likely to respond to hormonal therapy. Future trials should control prognostic factors that affect outcome. Patients should be stratified with respect to the disease status (advanced versus recurrent), the amount and type of previous treatment, the hormone receptor status, the histological type/grade, the performance status and the duration of hormonal treatment. Trials distinguishing the effects of hormonal treatment depending on the above characteristics may give more robust evidence to use bio-markers assessment as an adjunct in clinical practice. A similar example is the introduction of ER and PR assessments in the management of breast cancer.

As there is no evidence that current treatment modalities for advanced or recurrent endometrial cancer prolong survival significantly, the development of new agents may be required, although it is important that existing interventions and agents showing positive response in phase II studies are further tested in a prospective way in trials of adequate size and quality.

Acknowledgments

We thank Heather Dickinson for contributing to the writing of the protocol. We thank Chris Williams for clinical and editorial advice, Jane Hayes for designing the search strategy and Gail Quinn and Clare Jess for their contribution to the editorial process. We thank the referees for their helpful comments. We are grateful to Griffiths fund for supporting this project.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.

NHS Cochrane Collaboration Programme Grant Scheme CPG-506

CHARACTERISTICS OF STUDIES

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

Ayoub 1988

Methods	RCT (stratified)
Participants	Subset of 43 patients with stage IV and recurrent endometrial cancer from total study population of 262 patients

20 were randomised to chemotherapy and 23 to chemo-hormonal therapy Randomisation was stratified by the site of advanced disease (pelviabdominal versus distant metastases) The median age of the patients was 63 years (range: 40 to 74 years) Multiple centre trial from Canada		
Interventions	Intervention CAF (cyclophosphamide, adriamycin, 5-fluorouracil) and MPA (medroxyprogesterone acetate) 200 mg od for 3 weeks followed by tamoxifen (TMX) 20 mg for 3 weeks Control CAF only	
Outcomes	Overall survival Objective tumour response (complete/partial/stable/progression) Duration of remission	
Notes	The treatment groups were well balanced with respect to whether patients had received palliative radiation or not, prior to commencing chemo- or chemo-hormonal therapy The exact log rank P value from the Kaplan Meier plot was not reported so it was not possible to estimate the hazard ratio (Parmar 1998) From the KM plot, the median duration of follow up was 24 months “Hormonal therapy-related toxicity revealed a high incidence of phlebitis”	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Adequate sequence generation?	Low risk	“Eligible patients were prospectively randomized to chemotherapy or chemo-hormonal therapy after stratification on the basis of advanced pelviabdominal disease vs distant metastatic disease”
Allocation concealment?	Unclear risk	Not reported
Blinding? All outcomes	Unclear risk	Not reported
Incomplete outcome data addressed? All outcomes	Low risk	% analysed; 43/46 (93%) “Three patients refused to begin chemotherapy, so that 43 patients were evaluable”
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement
Free of other bias?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Accurate classifications of outcomes?	Low risk	“Response criteria were based on those suggested by the International Union against Cancer (UICC). Standard ECOG criteria were used to assess toxicity.”

Pandya 2001

Methods	RCT
Participants	<p>Multiple centre trial from USA 62 patients with advanced endometrial cancer 20 patients with advanced endometrial cancer were randomised to the megestrol group and 42 to the megestrol and tamoxifen group The median age in the megestrol arm was 68 years The median age in the megestrol and tamoxifen arm was 65 years 16 (26%) patients were less than 60 years of age, 26 patients (42%) were 61 to 70 years of age and 20 (32%) were over 70 years of age 32 (52%) women had Grade 1 and 2 disease, 29 (47%) had Grade 3 disease and Grade was unknown in 1 patient (2%) 22 (35%) women had performance status 'fully active', 29 (47%) had status 'ambulatory' and 11 (18%) had status 'in bed' 50%</p>

Interventions	Interventions: <ul style="list-style-type: none"> • Megestrol 80 mg bd orally • Megestrol 80 mg bd orally and tamoxifen 10 mg bd orally
Outcomes	Overall survival Response (complete/partial/no response)
Notes	<p>The megestrol arm was terminated early because of poor accrual</p> <p>There was no imbalance at baseline between the 2 groups</p> <p>Initial performance status is the only covariate that retained significance in the stepwise proportional hazards regression of survival</p> <p>The follow up ranged from 0 to 60 months</p> <p>The exact log rank P value from the Kaplan Meier plot was not reported so it was not possible to estimate the hazard ratio (Parmar 1998). We deduced death within 5 years from the Kaplan Meier plot and the number of reported deaths in each group</p> <p>The median survival time of ambulatory patients was 11.3 months compared to a median time of 3.5 months among the non ambulatory patients. The survival times on the megestrol arm ranged from 11 days to 60.6 months, with a median of 12 months, whereas the survival times on the megestrol and tamoxifen arm ranged from 48 days to 46.6 months, with a median of 8.6 months</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear	risk Not reported
Allocation concealment?	Low risk	"Patients were randomized at the Central Randomization Desk at the Eastern Cooperative Oncology Group Operations Office"
Blinding? All outcomes	Unclear risk	Not reported
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 62/62 (100%) 3 patients were unevaluable for response (Table 2)
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement
Free of other bias?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Accurate classifications of outcomes?	Low risk	"The disease must have been measurable, meaning that abdominal, pelvic, or other masses must have been defined in at least two dimensions by palpation or by computed tomography scan, but not by sonography; ascites and pleural effusion alone were not considered measurable"

Rendina 1984

Methods	Balanced prognostic study
Participants	93 patients with stage III or IV stage endometrial cancer 45 patients received tamoxifen (TMX) and 48 patients medroxyprogesterone acetate (MPA) Single-centre trial from Italy
Interventions	TMX 20 mg bd MPA 1g/week IM
Outcomes	1-year survival Side effects
Notes	It is not stated if the included patients received any treatment prior to enrolment (chemotherapy, radiotherapy or hormonal therapy)

45 patients received TMX and 48 patients MPA

In the TMX group 23 of the responders later relapsed and received combination therapy of TMX and MPA

In the MPA group 24 of the responders later relapsed and received combination therapy of TMX and MPA

The follow up was 1 year

Side effects were reported by treatment arm, but their categorisation was different and therefore not directly comparable:

“The side-effects with MPA were similar to those previously reported in the literature (Ganzina and Robustelli della Cuna, 1982) and included weight gain due to fluid retention (70%), facies lunaris (16%), tremors (14%), gluteal abscess (10%) and vaginal bleeding (10%). These and other reversible side-effects such as sweating, muscular cramps, thrombophlebitis and raised blood pressure were never severe enough to require withdrawal of therapy and the clinical tolerance to MPA treatment was generally good when compared to other agents used in oncology.

Treatment was not interrupted in any of the patients on TMX because of side-effects. Those reported were slight nausea (31%) and/or gastralgia (20%), anorexia (38%), urticarial skin reactions (22%), minimal transitory thrombocytopenia (16%) and transitory tumour flare in the first week of therapy in 91% of patients.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	“Treatment was allocated without a code, but always ensuring that the two groups were well balanced for age, menopausal status, disease-free interval and both stage and site of tumour.” Table 1 depicts patient characteristics by treatment arm”
Allocation concealment?	High risk	Not applicable
Blinding? All outcomes	Unclear risk	Not reported
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 93/93 (100%)
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement
Free of other bias?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Accurate classifications of outcomes?	Low risk	“The IUCC classification of response was used as shown below: Complete remission (CR), Complete disappearance of all evidence of neoplastic disease. Partial remission (PR), A 50% or more reduction in the diameters of all lesions and/or a 50% reduction in ascites or pleural effusion. No change (NC), No change in the size of lesions. Progressive disease (PD), A 50% or more increase in the diameters of all lesions and/or effusions or the appearance of new lesions. Tumour response was assessed by clinical examination and radiography (Hayward et al., 1977).”

Stolyarova 2001

Methods	RCT
Participants	Subset of 14 patients with stage III endometrial cancer from total study population of 76 patients 7 were randomised to radiotherapy plus 17-oxyprogesterone caproate (OPC) and 7 to radiotherapy only

Interventions	OPC and radiotherapy Radiotherapy
Outcomes	5-year disease-free survival
Notes	The duration of follow up was not reported 55.5% of 7 patients receiving radiotherapy with OPC were not disease-free 62.4% of 7 patients receiving radiotherapy alone were not disease-free For 5-year disease-free survival we deduced that there were 4 women in each group who relapsed using the following percentages given in the paper: 55.5% of 7 = 3.885 and 62.4% of 7 = 4.368. However, percentages should roughly correspond to integer numbers, unless there was loss to follow up which was not reported in the trial. Only possible % of women who relapsed by the end of trial could have been: 0% (0), 14.3% (1), 28.6% (2), 42.9% (3), 57.1% (4), 71.4% (5), 85.7% (6) and 100% (7)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported
Allocation concealment?	Unclear risk	Not reported
Blinding? All outcomes	Unclear risk	Not reported
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 14/14 (100%)
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement
Free of other bias?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Accurate classifications of outcomes?	Unclear risk	Not reported

Thigpen 1999

Methods	RCT
Participants	Multicentre trial from USA A group of 299 patients with advanced or recurrent endometrial adenocarcinoma and not amenable to control with surgery and/or radiotherapy were randomly allocated to therapy of low-dose (200 mg/d) MPA or high-dose (1000 mg/d) MPA 145 women with advanced or recurrent endometrial cancer were randomised to low-dose medroxyprogesterone acetate (MPA) and 154 patients to high-dose MPA 10 patients (3.3%) were less than 50 years of age, 52 patients (17.4%) were 50 to 59 years of age, 118 (39.5%) were 60 to 69 years of age, 97 (32.4%) were 70 to 79 years of age and 22 (7.4%) were 80 or more years of age 17 (5.7%) women had FIGO stage III, 68 (22.7%) stage IV and 214 (71.6%) had recurrent disease 59 (19.7%) women had Grade 1 disease, 113 (37.8%) had Grade 2 and 127 (42.5%) had Grade 3 disease Histology was adenocarcinoma in 107 (35.8%) women, endometrioid in 81 (27.1%), adenosquamous carcinoma in 38 (12.7%), papillary serous adenocarcinoma in 32 (10.7%), adenoacanthoma in 8 (2.7%), clear-cell carcinoma in 13 (4.3%) and the remaining 18 (6%) women had other histology 94 (31.5%) women had performance status 0, 137 (45.8%) had status 1 and 68 (22.7%) had status 2
Interventions	145 patients received MPA at dose 200 mg/d 154 patients received MPA at dose 1000 mg/d
Outcomes	Overall survival Response (complete/partial/no response) Progression-free survival Serum levels of MPA

Notes

There were no appreciable differences between the patients on the 2 regimens with regard to age, performance status, prior treatment with surgery and/or radiotherapy, stage, cell type, or histological grade. In addition, for the 132 patients who had data available for both oestrogen and progesterone receptors there were no appreciable differences observed between the 2 regimens with regard to receptor status

132 out of 145 women in the low-dose group died within 4 years, compared to 148 out of 154 in the high-dose group

134 out of 145 women in the low-dose group had disease progression within 4 years, compared to 150 out of 154 in the high-dose group

From the Kaplan Meier plot the duration of follow-up ranged from 0 to 48 months

Adjusted hazard ratios using Cox regression for overall and progression-free survival were reported. The Cox model was adjusted for the initial performance status, progesterone-receptor level, tumour grade and age

Thrombophlebitis was reported by treatment arm and it was similar in both groups: 5% of women in low-dose arm versus 4% in high-dose arm. 2% of women had Grade 3 or 4 thrombophlebitis in both the low-dose and high-dose group

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Treatment assignments were permuted randomly within blocks defined by the institutions and receptor status"
Allocation concealment?	Unclear risk	Not reported
Blinding? All outcomes	Unclear risk	Not reported
Incomplete outcome data addressed? All outcomes	Low risk	% analysed for adverse events: 299/299 (100%) For survival outcomes all patients were analysed using appropriate statistical techniques The denominators for the number of women with thrombophlebitis or other adverse events included the 3 women who were not analysed. This was due to details of these 3 women not being provided, but clearly this was unimportant to the results
Free of selective reporting?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Free of other bias?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Accurate classifications of outcomes?	Low risk	"Response was defined according to standard GOG criteria".

Urbanski 1993

Methods	RCT
Participants	Multicentre trial from USA Subset of 31 women with stage III endometrial cancer from a trial of 205 women with endometrial cancer of stage I-III 12 women were randomised to hydroprogesterone caproate and 19 to the control group The median age of the 205 women with endometrial cancer of all stages was 56 years with a range 41 to 80 years old
Interventions	Intervention: Adjuvant progestagen therapy: started 4 to 6 weeks after surgery and consisted of biweekly intra-muscular injections of 500 mg of hydroxy-progesterone caproate. For subjective reasons part of the patients received progestagens intraorally. The treatment was continued for 1 year Control: No adjuvant progestagen therapy
Outcomes	Overall survival Endometrial cancer-related deaths

	Cancer-related deaths Disease relapse	
Notes	In more than half of the patients histological diagnosis did not define histological grade Histological type and grade were not given by stage Patients with poor prognostic factors were treated postoperatively with external pelvic irradiation and/or intracavitary radium, however we do not know how many of those had stage III disease No patient was lost to follow up The duration of follow up in the trial was 60 months The exact log rank P value from the Kaplan Meier plot was not reported so it was not possible to estimate the hazard ratio (Parmar 1998) The overall 5-year survival rate by stage and treatment group was reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not reported, "Patients were randomly assigned to a control group or to a group receiving adjuvant Progestagen therapy"
Allocation concealment?	Unclear risk	Not reported
Blinding? All outcomes	Unclear risk	Not reported
Incomplete outcome data addressed? All outcomes	Low risk	% analysed: 31/31 (100%)
Free of selective reporting?	Unclear risk	Insufficient information to permit judgement
Free of other bias?	Unclear risk	Insufficient information to assess whether an additional risk of bias exists
Accurate classifications of outcomes?	Unclear risk	Not reported

CAF: cyclophosphamide, adriamycin, 5-fluorouracil

GOG: Gynecologic Oncology Group

IM: intramuscular

MPA: medroxyprogesterone acetate

OPC: 17-oxyprogesterone caproate

RCT: randomised controlled trial

TMX: tamoxifen

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Behling 1983	Randomised comparison of hormonal therapy versus no hormonal therapy in patients who had received primary radiotherapy was possible, but outcomes were not reported by staging
Bruera 1998	Randomised, double-blind, cross-over trial of megestrol acetate versus placebo in patients with advanced cancer (37 were women: 7 had cancer of the genitourinary tract and of those the number of endometrial cancer cases was unknown). Survival was not reported since a cross-over design is not appropriate for survival outcomes. Quality of life was an outcome in the trial, but was not reported by treatment group and cancer type
Carey 2006	Systematic review that yielded no further included trials
Cohen 1984	This study was excluded because it was not clear which patients were randomised and evaluated. In regimen 1, there were 63 patients assigned with abnormal cardiac status in order to avoid the possibility of adriamycin cardiotoxicity from regimen 2. Consequently, patients were not randomly assigned. The results are presented as a whole cohort

COSA trial	The authors could not provide us the data regarding: 1) the number of women with stage III disease who died and had disease progression or relapsed at any reported time points in each of the groups, 2) the hazard ratio (and 95% CI) for overall survival and recurrence or progression-free survival for the 57 women with stage III disease
Decruze 2007	Systematic review that yielded no further included trials
Deng 2000	Outcomes were not reported by staging. Table 2 depicts the number of women whose tumour disappeared and this includes women with stage I disease only. It is unclear whether a proportion of the remaining 16 women in the hormonal group had advanced stage disease
Humber 2005	Systematic review that yielded no further included trials
Kneale 1988	Letter to the authors of the trial of Macdonald 1988
Krafft 1990	Only 5/196 patients in the trial had advanced stage disease and outcomes not reported by stage
Lentz 1996	Not a RCT
Lotze 1982	There are only 10 women in the comparison group. The only relevant results are in the figure, which is difficult to interpret. It has been done by life-table method, but if the horizontal lines were drawn from each point to each death, and then vertical lines, it would look more like a Kaplan-Meier plot. The weakness are: 1) they obviously only checked for deaths at yearly intervals(a proper K-M plot would use the exact date of death); and 2) it was not clear how long women were followed up for and they may have been followed up for different lengths of time in the 2 groups In the combination chemotherapy + hormonal treatment arm, 8 women had complete remission but of these 2 died of second malignancies and one of the effects of radiotherapy. Presumably, the 2 women who did not have complete remission also died, but this is not explicitly stated. From the figure, it looks like 1 woman was dead at 1 year, another 2 at 2 years and another 2 at 3 years. 5-year cumulative survival (calculated using life-table methods) was 65% In the hormonal only group, 26 women had complete remission, 17 had partial remission, 16 had disease progression Among all women, 33 were alive at 31 December 1981, so presumably 28 died in the hormonal only arm
Macdonald 1988	Only 26 out of 346 patients had advanced stage disease Outcomes not reported by treatment and stage
Martin-Hirsch 1996	Systematic review that yielded no further included trials
Martin-Hirsch 1999	Systematic review of progestagen therapy following primary surgery after endometrial cancer that yielded no further included trials
Piver 1980	Not a RCT. It appears from the abstract to be a prospective trial, however, the materials and methods sections states that "forty-four patients with metastatic endometrial adenocarcinoma received Depo-Provera over a five and a half year period compared to 70 controls who received Delalutin over the previous eleven and a half years". This suggests that the groups were not concurrent and that historical controls were used
Polyzos 2006	Systematic review that yielded Piver 1986: it was not included because the trial randomised a subset of 18 patients and it was later discontinued and did not report outcomes specified in our protocol for the randomised patients
Vavra 1990	The outcomes of 5 patients with stage II/III disease were jointly reported
Vishnevsky 1993	66 out of 540 patients had stage III disease, but outcomes were not reported by staging
Zhang 1996	Outcomes specified in our protocol were not reported in trial

RCT: randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

Bloss

Trial name or title	Combination chemotherapy compared with hormone therapy in treating patients with recurrent, stage III or stage IV endometrial cancer
Methods	Randomised phase III trial

Participants	Patients with recurrent, stage III, or stage IV endometrial cancer
Interventions	Biological: filgrastim Drug: cisplatin Drug: megestrol acetate Drug: paclitaxel Drug: tamoxifen citrate
Outcomes	Progression-free survival Response Determine if progesterone status provides information on whether patients are more likely to benefit from chemotherapy Toxicity profiles Quality of life
Starting date	May 2001
Contact information	Jeffrey D. Bloss, MD, Study Chair, Siteman Cancer Center at Barnes-Jewish Hospital - Saint Louis
Notes	Study completed - no published results yet. Preliminary results regarding survival requested from the Study Chair

DATA AND ANALYSES

Comparison 1

MPA versus tamoxifen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death within 1 year	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 2

CAF and MPA followed by tamoxifen versus CAF alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death within 2 years	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 3

Adjuvant progestagen therapy versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death within 5 years	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 4

High-dose MPA versus low-dose MPA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Progression-free survival	1		Hazard Ratio (Random, 95% CI)	Subtotals only
3 Thrombophlebitis	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 5

Megestrol and tamoxifen versus megestrol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death within 5 years	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 6

OPC and radiotherapy versus radiotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 5-year disease-free survival	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 MPA versus tamoxifen, Outcome 1 Death within 1 year

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 1 MPA versus tamoxifen

Outcome: 1 Death within 1 year

Analysis 2.1. Comparison 2 CAF and MPA followed by tamoxifen versus CAF alone, Outcome 1 Death within 2 years

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 2 CAF and MPA followed by tamoxifen versus CAF alone

Outcome: 1 Death within 2 years

Analysis 3.1. Comparison 3 Adjuvant progestagen therapy versus control, Outcome 1 Death within 5 years

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 3 Adjuvant progestagen therapy versus control

Outcome: 1 Death within 5 years

Analysis 4.1. Comparison 4 High-dose MPA versus low-dose MPA, Outcome 1 Overall survival

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 4 High-dose MPA versus low-dose MPA

Outcome: 1 Overall survival

Analysis 4.2. Comparison 4 High-dose MPA versus low-dose MPA, Outcome 2 Progression-free survival

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 4 High-dose MPA versus low-dose MPA

Outcome: 2 Progression-free survival

Analysis 4.3. Comparison 4 High-dose MPA versus low-dose MPA, Outcome 3 Thrombophlebitis

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 4 High-dose MPA versus low-dose MPA

Outcome: 3 Thrombophlebitis

Analysis 5.1. Comparison 5 Megestrol and tamoxifen versus megestrol, Outcome 1 Death within 5 years

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 5 Megestrol and tamoxifen versus megestrol

Outcome: 1 Death within 5 years

Analysis 6.1. Comparison 6 OPC and radiotherapy versus radiotherapy alone, Outcome 1 5-year disease-free survival

Review: Hormonal therapy in advanced or recurrent endometrial cancer

Comparison: 6 OPC and radiotherapy versus radiotherapy alone

Outcome: 1 5-year disease-free survival

Appendix 1. MEDLINE search strategy

MEDLINE Ovid May week 2 2009

1. exp Endometrial Neoplasms/
2. (endometri* adj5 (neoplasm* or tumor* or tumour* or cancer* or malignan* or carcinom*)),mp.
3. exp Endometrial Hyperplasia/

4. (endometri* adj5 hyperplasia).mp.
5. 1 or 2 or 3 or 4
6. exp Antineoplastic Agents, Hormonal/
7. (antineoplastic adj5 hormon*).mp.
8. exp Progestins/
9. progest*.mp.
10. exp Receptors, Estrogen/
11. (estrogen adj5 receptor*).mp.
12. exp Receptors, Progesterone/
13. (progesterone adj5 receptor*).mp.
14. exp Aromatase Inhibitors/
15. (aromatase adj5 inhibit*).mp.
16. exp Selective Estrogen Receptor Modulators/
17. exp Gonadotropin-Releasing Hormone/
18. (gonadotropin-releasing adj hormone*).mp.
19. (gonadotropin adj releasing adj hormone*).mp.
20. (luteinizing adj hormone-releasing adj hormone*).mp.
21. (luteinizing adj hormone adj releasing adj hormone*).mp.
22. exp Intrauterine Devices, Medicated/
23. (intrauterine device* adj5 (hormon* or progest*)).mp.
24. tamoxifen.mp.
25. megestrol.mp.
26. medroxyprogesterone.mp.
27. arzoxifene.mp.
28. goserelin.mp.
29. leuprolide.mp.
30. letrozole.mp.
31. anastrozole.mp.
32. exemestane.mp.
33. hydroxyprogesterone.mp.
34. aminoglutethimide.mp.
35. (hormon* adj5 (therap* or treatment*)).mp.

36. or/6-35
37. 5 and 36
38. randomized controlled trial.pt.
39. controlled clinical trial.pt.
40. randomized.ab.
41. placebo.ab.
42. drug therapy.fs.
43. randomly.ab.
44. trial.ab.
45. groups.ab.
46. exp Cohort Studies/
47. cohort*.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
48. exp Retrospective Studies/
49. (case* and series).mp.
50. or/38-49
51. 37 and 50
52. (animals not (humans and animals)).sh.
53. 51 not 52

key: mp = title, original title, abstract, name of substance word, subject heading word

pt = publication type

ab = abstract

sh = subject heading

Appendix 2. EMBASE Search Strategy

EMBASE Ovid 1980 to 2009 week 20

1. exp Endometrium Tumor/
2. (endometri* adj5 (neoplasm* or tumor* or tumour* or cancer* or malignan* or carcinom*)).mp.
3. exp Endometrium Hyperplasia/
4. (endometri* adj5 hyperplasia).mp.
5. 1 or 2 or 3 or 4

6. exp “Antineoplastic Hormone Agonists and Antagonists”/
7. (antineoplastic adj5 hormon*).mp.
8. exp Gestagen/
9. progest*.mp.
10. Estrogen Receptor/
11. (estrogen adj5 receptor*).mp.
12. exp Progesterone Receptor/
13. (progesterone adj5 receptor*).mp.
14. exp Aromatase Inhibitor/
15. (aromatase adj5 inhibit*).mp.
16. exp Selective Estrogen Receptor Modulator/
17. exp Gonadorelin/
18. (gonadotropin-releasing adj hormone*).mp.
19. (gonadotropin adj releasing adj hormone*).mp.
20. (luteinizing adj hormone-releasing adj hormone*).mp.
21. (luteinizing adj hormone adj releasing adj hormone*).mp.
22. exp Intrauterine Contraceptive Device/
23. (intrauterine device* adj5 (hormon* or progest*)).mp.
24. tamoxifen.mp.
25. megestrol.mp.
26. medroxyprogesterone.mp.
27. arzoxifene.mp.
28. goserelin.mp.
29. leuprolide.mp.
30. letrozole.mp.
31. anastrozole.mp.
32. exemestane.mp.
33. hydroxyprogesterone.mp.
34. aminoglutethimide.mp.
35. (hormon* adj5 (therap* or treatment*)).mp.
36. or/6-35
37. exp controlled clinical trial/

38. randomized.ab.
39. placebo.ab.
40. dt.fs.
41. randomly.ab.
42. trial.ab.
43. groups.ab.
44. exp cohort analysis/
45. cohort*.mp.
46. exp Retrospective Study/
47. exp Prospective Study/
48. (case* and series).mp.
49. or/37-48
50. 49 and 36 and 5
51. exp Animal/
52. Human/
53. 51 not (51 and 52)
54. 50 not 53

key: mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

ab = abstract

fs = floating subheading

Appendix 3. CENTRAL search strategy

CENTRAL, *The Cochrane Library* Issue 2, 2009

1. MeSH descriptor Endometrial Neoplasms explode all trees
2. endometri* near/5 (neoplasm*or tumor* or tumour* or cancer* or malignan* or carcinom*)
3. MeSH descriptor Endometrial Hyperplasia explode all trees
4. endometri* near/5 hyperplasia
5. (#1 OR #2 OR #3 OR #4)
6. MeSH descriptor Antineoplastic Agents, Hormonal explode all trees
7. antineoplastic near/5 hormon*

8. MeSH descriptor Progestins explode all trees
9. progest*
10. MeSH descriptor Receptors, Estrogen explode all trees
11. estrogen near/5 receptor*
12. MeSH descriptor Receptors, Progesterone explode all trees
13. progesterone near/5 receptor*
14. MeSH descriptor Aromatase Inhibitors explode all trees
15. aromatase near/5 inhibit*
16. MeSH descriptor Selective Estrogen Receptor Modulators explode all trees
17. MeSH descriptor Gonadotropin-Releasing Hormone explode all trees
18. gonadotropin next releasing next hormone*
19. gonadotropin-releasing next hormone*
20. luteinizing next hormone-releasing next hormone*
21. luteinizing next hormone next releasing next hormone*
22. MeSH descriptor Intrauterine Devices, Medicated explode all trees
23. intrauterine device* near/5 (hormon* or progest*)
24. tamoxifen
25. megestrol
26. medroxyprogesterone
27. arzoxifene
28. goserelin
29. leuprolide
30. letrozole
31. anastrozole
32. exemestane
33. hydroxyprogesterone
34. aminoglutethimide
35. hormon* near/5 (therap* or treatment*)
36. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
37. (#5 AND #36)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the Types of participants section it was originally specified that, “patients must have no history of any other malignancy (except basal cell carcinoma)”, but this constraint was later removed as it was not reported in most trials.

Restriction to RCTs

We restricted the review to RCTs once they were identified from the search results as these provide the best level of evidence. In the protocol we had stated the following as we did not expect to find any RCTs:

“Since we expect to find few RCTs, non-randomised studies with concurrent comparison groups will be included:

- Quasi-randomised trials, non-randomised trials, prospective and retrospective cohort studies, and case series of 30 or more patients.

Case-control studies and case series of fewer than 30 patients will be excluded”.

Risk of bias

Risk of bias was not examined in non-randomised studies as the review was restricted to RCTs. We had initially stated that we would apply the following risk of bias criteria to non-randomised studies:

“The risk of bias in non-randomised studies will be assessed in accordance with four additional criteria:

Cohort selection

1. Were relevant details of criteria for assignment of patients to treatments provided?
 - i) Yes
 - ii) No
 - iii) Unclear
2. Was the group of women who received hormonal therapy (experimental intervention) representative of the general patient population?
 - i) Yes, if they were representative of women with advanced or recurrent endometrial cancer
 - ii) No, if group of patients was selected
 - iii) Unclear, if selection of group was not described
3. Was the group of women who received the comparison intervention representative?
 - i) Yes, if drawn from the same population as the intervention group
 - ii) No, if drawn from a different source

iii) Unclear, if selection of group not described

Comparability of treatment groups

1. Were there no differences between the two groups or were differences controlled for, in particular with reference to age, FIGO stage, histology, tumour grade, performance status, previous treatment?
 - i) Yes, if at least two of these characteristics were reported and any reported differences were controlled for
 - ii) No, if the two groups differed and differences were not controlled for.
 - iii) Unclear, if fewer than two of these characteristics were reported even if there were no other differences between the groups, and other characteristics had been controlled for”.

Continuous outcome data

Continuous outcome data were not reported in any of the trials so the following sections in the protocol which discussed the handling of data for continuous outcomes were removed as they were unnecessary:

“Data extraction and management

- For continuous outcomes (e.g. quality of life measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

Measures of treatment effect

- For time to event data, we will use the HR, if possible. The HR summarises the chances of survival in women who received one type of treatment compared to the chances of survival in women who received another type of treatment. However, the logarithm of the HR, rather than the HR itself, is generally used in meta-analyses”.

Data synthesis

The review was restricted to single-trial analyses so it was not possible to perform meta-analyses. Therefore it was not relevant to assess heterogeneity between results of trials and we were unable to assess reporting biases using funnel plots or conduct any subgroup analyses or sensitivity analyses. The following sections of the protocol were therefore removed:

“Assessment of heterogeneity

Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the

heterogeneity (Deeks 2001) and, where possible, by sub-group analyses (see Subgroup analysis and investigation of heterogeneity). If there was evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases

Funnel plots corresponding to meta-analysis of the primary outcome will be examined for evidence of small study effects. If such evidence exists, publication bias and other possible explanations will be considered. If funnel plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models.

Data synthesis

If sufficient, clinically similar studies are available, their results will be pooled in meta-analyses. Adjusted summary statistics will be used if available; otherwise unadjusted results will be used.

- For time-to-event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, the RR will be calculated for each study and these will then be pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.

If any trials have multiple intervention groups, the control group will be divided between the intervention groups - to prevent double counting of participants in the meta-analysis - and comparisons between each intervention and a split control group will be treated independently. This is .

Random effects models with inverse variance weighting will be used for all meta-analyses (DerSimonian 1986).

If sufficient data are available, indirect comparisons, using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other.

Subgroup analysis and investigation of heterogeneity

Sub-group analyses will be performed, grouping the trials by 'type of hormonal treatment used and type of receptor'.

Factors such as age, stage, type of intervention, length of follow-up, adjusted/unadjusted analysis will be considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analyses will be performed (i) excluding non-randomised studies if RCTs have been included (ii) excluding studies at high risk of bias and (iii) using unadjusted results".

WHAT'S NEW

Last assessed as up-to-date: 9 November 2010.

Date	Event	Description
27 March 2014	Amended	Contact details updated.

References to studies included in this review

* *Indicates the major publication for the study*

- Ayoub 1988 {published data only} . Ayoub J, Audet-Lapointe P, Méthot Y, Hanley J, Beaulieu R, Chemaly R, et al. Efficacy of sequential cyclical hormonal therapy in endometrial cancer and its correlation with steroid hormone receptor status. *Gynecologic Oncology*. 1988; 31(2):327–37. [PubMed: 2971597]
- Pandya 2001 {published data only} . Pandya KJ, Yeap B, Y Weiner LM, Krook JE, Erban JK, Schinella RA, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). *American Journal of Clinical Oncology*. 2001; Vol. 24(issue 1):43–6. [PubMed: 11232948]
- Rendina 1984 {published data only} . Rendina GM, Donadio C, Fabri M, Mazzoni P, Nazzicone P. Tamoxifen and medroxyprogesterone therapy for advanced endometrial carcinoma. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 1984; Vol. 17(issue 4):285–91.
- Stolyarova 2001 {published data only} . Stolyarova I, Minaev A. Effect of hormonotherapy on the results of radiation treatment in patients with endometrial carcinoma. *Journal of B.U.On*. 2001; Vol. 6(issue 3):271–4.
- Thigpen 1999 {published data only} . Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *Journal of Clinical Oncology*. 1999; Vol. 17(issue 6):1736–44. [PubMed: 10561210]
- Urbanski 1993 {published data only} . Urbanski K, Karolewski K, Kojs Z, Klimek M, Dyba T. Adjuvant progestagen therapy improves survival in patients with endometrial cancer after hysterectomy. Results of one-institutional prospective clinical trial. *European Journal of Gynaecological Oncology*. 1993; 14(Suppl):98–104. [PubMed: 8200383]

References to studies excluded from this review

- Behling 1983 {published data only} . Behling H, Krafft W, Schmeisser G, Schirmer A, Preibsch W, Brückmann D. Effectivity of long-term high dose norethisterone treatment of corpus uteri carcinoma patients. Results of a prospective randomized study. *Zentralblatt für Gynäkologie*. 1983; 105(9):553–9. [PubMed: 6880470]
- Bruera 1998 {published data only} . Bruera E, Ernst S, Hagen N, Spachynski K, Belzile M, Hanson J, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prevention and Control*. 1998; 2(2):74–8. [PubMed: 9765767]
- Carey 2006 {published data only} . Carey MS, Gawlik C, Fung-Kee-Fung M, Chambers A, Oliver T, Cancer Care Ontario Practice Guidelines Initiative Gynecology Cancer Disease Site Group. Systematic review of systemic therapy for advanced or recurrent endometrial cancer. *Gynecologic Oncology*. 2006; 101(1):158–67. [PubMed: 16434086]
- Cohen 1984 {published data only} . Cohen CJ, Bruckner HW, Deppe G, Blessing JA, Homesley H, Lee JH, et al. Multidrug treatment of advanced and recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Obstetrics and Gynecology*. 1984; 63(5):719–26. [PubMed: 6371627]

- COSA trial {published data only} . Quinn MA, COSA-NZ-UK Endometrial Cancer Study Groups. Adjuvant medroxyprogesterone acetate in high-risk endometrial cancer. *International Journal of Gynecological Cancer*. 1998; 8:387–91.
- Decruze 2007 {published data only} . Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. *International Journal of Gynecological Cancer*. 2007; 17(5):964–78. [PubMed: 17442022]
- Deng 2000 {published data only} . Deng XH, Duan W, Li BZ. Estramustine phosphate in the treatment of endometrium carcinoma. *Chinese Journal of Cancer Research*. 2000; 12(1):58–63.
- Humber 2005 {published data only} . Humber C, Tierney J, Symonds P, Collingwood M, Kirwan J, Williams C, et al. Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma. *Cochrane Database of Systematic Reviews*. 2005; (Issue 4) [Art. No.: CD003915. DOI: 10.1002/14651858.CD003915.pub3].
- Kneale 1988 {published data only} . Kneale BL, Quinn MA, Rennie GC. A randomized trial of progestogens in the primary treatment of endometrial carcinoma. *British Journal of Obstetrics & Gynaecology*. 1988; 95(8):828. [PubMed: 3048376]
- Krafft 1990 {published data only} . Krafft W, Steuckardt R, König EM, Schirmer A, Schmeisser G, Brückmann D. Efficacy of an adjuvant norethisterone acetate therapy (NEA) of endometrial carcinoma treated with primary surgery or irradiation. *Zentralblatt für Gynäkologie*. 1990; Vol. 112(issue 16):1023–30. [PubMed: 2220176]
- Lentz 1996 {published data only} . Lentz S, Brady M, Major F, Reid G, Soper J. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *Journal of Clinical Oncology*. 1996; 14(2):357–61. [PubMed: 8636744]
- Lotze 1982 {published data only} . Lotze W, Richter P, Sarembe B. High-dose progesterone therapy in advanced endometrial cancer. *Archiv für Geschwulstforschung*. 1982; Vol. 52(issue 7):569–74. [PubMed: 6187310]
- Macdonald 1988 {published data only} . Macdonald RR, Thorogood J, Mason MK. A randomized trial of progestogens in the primary treatment of endometrial carcinoma. *British Journal of Obstetrics and Gynaecology*. 1988; 95(2):166–74. [PubMed: 2964861]
- Martin-Hirsch 1996 {published data only} . Martin-Hirsch PL, Lilford RJ, Jarvis GJ. Adjuvant progestagen therapy for the treatment of endometrial cancer: review and meta-analyses of published randomised controlled trials. *European Journal of Obstetrics, Gynecology, & Reproductive Biology*. 1996; 65(2):201–7.
- Martin-Hirsch 1999 {published data only} . Martin-Hirsch PL, Jarvis G, Kitchener H, Lilford R. Progestagens for endometrial cancer. *Cochrane Database of Systematic Reviews*. 1999; (Issue 4) [Art. No.: CD001040. DOI: 10.1002/14651858.CD001040].
- Piver 1980 {published data only} . Piver MS, Barlow JJ, Lurain JR, Blumenson LE. Medroxyprogesterone Acetate (Depo-Provera) Vs. Hydroxyprogesterone Caproate (Delalutin) in Women with Metastatic Endometrial Adenocarcinoma. *Cancer*. 1980; 45:268–72. [PubMed: 6985833]
- Polyzos 2006 {published data only} . Polyzos NP, Pavlidis N, Paraskevaidis E, Ioannidis JP. Randomized evidence on chemotherapy and hormonal therapy regimens for advanced endometrial cancer: an overview of survival data. *European Journal of Cancer*. 2006; 42(3):319–26. [PubMed: 16376072]
- Vavra 1990 {published data only} . Vavra N, Salzer H, Sevela P, Breitenacker G, Czerwenka K, Kucera H. Adjuvant hormone therapy in endometrial carcinoma: medroxyprogesterone acetate versus tamoxifen-medroxyprogesterone acetate sequential therapy. *Gynäkologische Rundschau*. 1990; Vol. 30(issue 3):133–43. [PubMed: 2147161]
- Vishnevsky 1993 {published data only} . Vishnevsky AS, Bokhman YaV, Loutfi G. Favourable influence of adjuvant hormone therapy by oxyprogesterone caproate (OPC) and by its combination with tamoxifen on 5-year survival rate of surgical and combined treatment of primary endometrial carcinoma patients. *European Journal of Gynaecological Oncology*. 1993; Vol. 14(issue 2):150–3. [PubMed: 8500499]
- Zhang 1996 {published data only} . Zhang X, Cao B. Exploration for drug therapy in endometrial carcinoma. *Chinese Medical Journal*. 1996; 109(5):356–60. [PubMed: 9208491]

References to ongoing studies

- Bloss {published data only} . Bloss JD. Combination chemotherapy compared with hormone therapy in treating patients with recurrent, stage III, or stage IV endometrial cancer. <http://clinicaltrials.gov/ct2/show/NCT00016341?term=NCT00016341&rank=1>

Additional references

- Aalders 1984 . Aalders JG, Abeler V, Kolstad P. Clinical (stage III) as compared to subclinical intrapelvic extrauterine tumor spread in endometrial carcinoma: a clinical and histopathological study of 175 patients. *Gynecologic Oncology*. 1984; 17(1):64–74. [PubMed: 6693053]
- Ackerman 1996 . Ackerman I, Malone S, Thomas G, Franssen E, Balogh J, Dembo A. Endometrial carcinoma - relative effectiveness of adjuvant irradiation vs therapy reserved for relapse. *Gynecologic Oncology*. 1996; 60(2):177–83. [PubMed: 8631535]
- Armstrong 1975 . Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *International Journal of Cancer*. 1975; 15(4):617–31.
- Asbury 2002 . Asbury RF, Brunetto VL, Lee RB, Reid G, Rocereto TF. Goserelin acetate as treatment for recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *American Journal of Clinical Oncology*. 2002; 25(6):557–60. [PubMed: 12477997]
- Berek 2005 . Berek JS, Hacker NF. *Practical Gynecologic Oncology*. 4th Edition. Williams and Wilkins; Lippincott: 2005.
- Bonte 1981 . Bonte J, Ide P, Billiet G, Wynants P. Tamoxifen as a possible chemotherapeutic agent in endometrial adenocarcinoma. *Gynecologic Oncology*. 1981; 11(2):140–61. [PubMed: 6783481]
- Bucher 1997 . Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology*. 1997; 50(6):683–91. [PubMed: 9250266]
- Burke 2003 . Burke TW, Walker CL. Arzoxifene as therapy for endometrial cancer. *Gynecologic Oncology*. 2003; 90(2.2):S40–6. [PubMed: 12928005]
- Carlson 1984 . Carlson JA, Allegra JC, Day TG Jr, Wittliff JL. Tamoxifen and endometrial carcinoma: alterations in estrogen and progesterone receptors in untreated patients and combination hormonal therapy in advanced neoplasia. *American Journal of Obstetrics and Gynecology*. 1984; 149:149–53. [PubMed: 6232850]
- Chang 2008 . Chang S, Masse LC, Moser RP, Dodd KW, Arganaraz F, Fuemmler BF. State ranks of incident cancer burden due to overweight and obesity in the United States. *Obesity*. 2008; 16(7):1636–50. [PubMed: 18421271]
- Covens 1997 . Covens A, Thomas G, Shaw P, Ackerman I, Osborne R, Lukka H. A phase II study of leuprolide in advanced/recurrent endometrial cancer. *Gynecologic Oncology*. 1997; 64(1):126–9. [PubMed: 8995560]
- Covens 2003 . Covens A, Brunetto VL, Markman M, Orr JW, Lentz SS, Benda J. Phase II trial of danazol in advanced, recurrent, or persistent endometrial cancer: a Gynecologic Oncology Group study. *Gynecologic Oncology*. 2003; 89(3):470–4. [PubMed: 12798713]
- CTCAE 2006 . CTCAE. Common Terminology Criteria for Adverse Events. Vol. Vol. v3.0. CTCAE; [9 August 2006]
- Decruze 2007 . Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. *International Journal of Gynecologic Cancer*. 2007; 17(5):964–78.
- Deeks 2001 . Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M.; Davey Smith, G.; Altman, DG., editors. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd edition. BMJ Publication Group; London: 2001.
- DerSimonian 1986 . DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials*. 1986; 7:177–88. [PubMed: 3802833]

- Edmonson 1986 . Edmonson JH, Krook JE, Hilton JF, Long HJ, Cullinan SA, Everson L, et al. Ineffectiveness of tamoxifen in advanced endometrial carcinoma after failure of progestin treatment. *Cancer Treatment Reports*. 1986; 70(8):1019–20. [PubMed: 3731147]
- Farquhar 2009 . Farquhar CM, Marjoribanks J, Lethaby A, Lamberts Q, Suckling JA. Long term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database of Systematic Reviews*. 2009; (Issue 2) [Art. No.: CD004143. DOI: 10.1002/14651858.CD004143.pub3].
- Fiorica 2004 . Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecologic Oncology*. 2004; 92(1):10–4. [PubMed: 14751131]
- Gallagher 1991 . Gallagher CJ, Oliver RT, Oram DH, Fowler CG, Blake PR, Mantell BS. A new treatment for endometrial cancer with gonadotrophin releasing-hormone analogue. *British Journal of Obstetrics and Gynaecology*. 1991; 98(10):1037–41. [PubMed: 1751436]
- Geisler 1973 . Geisler H. The use of megestrol acetate in the treatment of advanced malignant lesions of the endometrium. *Gynecologic Oncology*. 1973; 1:340–4.
- GLOBOCAN 2002 . Ferlay, J.; Bray, F.; Pisani, P.; Parkin, DM.; GLOBOCAN. IARC CancerBase No. 5. 2.0. IARC Press; Lyon: 2002. Cancer Incidence, Mortality and Prevalence Worldwide. 2004
- Hald 1983 . Hald I, Salimtschik M, Mouridsen HT. Tamoxifen treatment of advanced endometrial carcinoma. A phase II study. *European Journal of Gynaecological Oncology*. 1983; 4(2):83–7. [PubMed: 6873094]
- Higgins 2003 . Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–60. [PubMed: 12958120]
- Higgins 2008 . Higgins, JPT.; Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration; 2008. Available from www.cochrane-handbook.org
- Hill 1996 . Hill HA, Austin H. Nutrition and endometrial cancer. *Cancer Causes and Control*. 1996; 7(1):19–32. [PubMed: 8850432]
- Hoffman 1989 . Hoffman MS. Treatment of recurrent and metastatic endometrial cancer with cisplatin, doxorubicin, cyclophosphamide, and megestrol acetate. *Gynecologic Oncology*. 1989; 35(1):75–7. [PubMed: 2477317]
- Jemal 2008 . Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. *Cancer Statistics, 2008*. CA: A Cancer Journal for Clinicians. 2008; 58:71–96. [PubMed: 18287387]
- Jeyarajah 1996 . Jeyarajah AR, Gallagher CJ, Blake PR, Oram DH, Dowsett M, Fisher C. Long-term follow-up of gonadotrophin-releasing hormone analog treatment for recurrent endometrial cancer. *Gynecologic Oncology*. 1996; 63(1):47–52. [PubMed: 8898167]
- Jick 1979 . Jick H, Watkins RN, Hunter JR, Dinan BJ, Madsen S, Rothman KJ. Replacement estrogens and endometrial cancer. *New England Journal of Medicine*. 1979; 300(5):218–22. [PubMed: 759868]
- Kaaks 2002 . Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. *Cancer Epidemiology, Biomarkers and Prevention*. 2002; 11(12): 1531–43.
- Kauppila 1984 . Kauppila A. Progestin therapy of endometrial, breast and ovarian carcinoma. A review of clinical observations. *Acta Obstetrica et Gynecologica Scandinavica*. 1984; 63(5): 441–50. [PubMed: 6238499]
- Kelley 1965 . Kelley RM, Baker WH. The role of progesterone in endometrial cancer. *Cancer Research*. 1965; 25(7):1190–2. [PubMed: 5843268]
- Kitchener 2008 . Kitchener HC. Survival from endometrial cancer in England and Wales up to 2001. *British Journal of Cancer*. 2008; 99(Suppl 1):S68–9. [PubMed: 18813265]
- Kohorn 1976 . Kohorn EI. Gestagens and endometrial carcinoma. *Gynecologic Oncology*. 1976; 4(4):398–411. [PubMed: 1001988]

- Lentz 1996 . Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. *Journal of Clinical Oncology*. 1996; 14(2):357–61. [PubMed: 8636744]
- Levine 1998 . Levine RL, Cargile CB, Blazes MS, van Rees B, Kurman RJ, Ellenson LH. PTEN mutations and microsatellite instability in complex atypical hyperplasia, a precursor lesion to uterine endometrioid carcinoma. *Cancer Research*. 1998; 58(15):3254–8. [PubMed: 9699651]
- Lindemann 2008 . Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *British Journal of Cancer*. 2008; 98(9): 1582–5. [PubMed: 18362938]
- Lovecchio 1984 . Lovecchio JL, Averette HE, Lichtinger M, Townsend PA, Girtanner RW, Fenton AN. Treatment of advanced or recurrent endometrial adenocarcinoma with cyclophosphamide, doxorubicin, cis-platinum, and megestrol acetate. *Obstetrics & Gynecology*. 1984; 63(4):557–60. [PubMed: 6538327]
- Ma 2004 . Ma BB, Oza A, Eisenhauer E, Stanimir G, Carey M, Chapman W. The activity of letrozole in patients with advanced or recurrent endometrial cancer and correlation with biological markers - a study of the National Cancer Institute of Canada Clinical Trials Group. *International Journal of Gynecologic Cancer*. 2004; 14(4):650–8.
- Markman 1997 . Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J. Leuprolide in the treatment of endometrial cancer. *Gynecologic Oncology*. 1997; 66(3):542. [PubMed: 9299275]
- Markman 2004 . Markman M. Hormonal therapy of endometrial cancer. *European Journal of Cancer*. 2005; 41(5):673–5. [PubMed: 15763641]
- McMeekin 2003 . McMeekin DS, Gordon A, Fowler J, Melemed A, Buller R, Burke T. A phase II trial of arzoxifene, a selective estrogen response modulator, in patients with recurrent or advanced endometrial cancer. *Gynecologic Oncology*. 2003; 90(1):64–9. [PubMed: 12821343]
- Moore 1991 . Moore TD, Phillips PH, Nerenstone SR, Cheson BD. Systemic treatment of advanced and recurrent endometrial carcinoma: current status and future directions. *Journal of Clinical Oncology*. 1991; 9(6):1071–88. [PubMed: 2033421]
- Obel 2006 . Obel JC, Friberg G, Fleming GF. Chemotherapy in endometrial cancer. *Clinical Advances in Hematology and Oncology*. 2006; 4(6):459–68. [PubMed: 16981669]
- Parmar 1998 . Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine*. 1998; 17(24): 2815–34. [PubMed: 9921604]
- Piver 1980 . Piver MS, Lele S, Barlow JJ. Melphalan, 5-fluorouracil, and medroxyprogesterone acetate in metastatic or recurrent endometrial carcinoma. Preliminary report. *Obstetrics and Gynecology*. 1980; 56(3):370–2. [PubMed: 7422177]
- Piver 1986 . Piver S, Lele S, Patsner B, Emrich L. Melphalan, 5-fluorouracil, and medroxyprogesterone acetate in metastatic endometrial carcinoma. *Obstetrics and Gynecology*. 1986; 67(2):261–4. [PubMed: 3945437]
- Podratz 1985 . Podratz KC, O'Brien PC, Malkasian GD, Decker DG, Jefferies JA, Edmonson JH. Effects of progestational agents in treatment of endometrial carcinoma. *Obstetrics and Gynecology*. 1985; 66(1):106–10. [PubMed: 4011061]
- Quinn 1989 . Quinn MA, Campbell JJ. Tamoxifen therapy in advanced/recurrent endometrial carcinoma. *Gynecologic Oncology*. 1989; 32(1):1–3. [PubMed: 2909443]
- Reifenstein 1974 . Reifenstein EC. The treatment of advanced endometrial cancer with hydroxyprogesterone caproate. *Gynecologic Oncology*. 1974; 2(2-3):377–414. [PubMed: 4616884]
- Rose 2000 . Rose PG, Brunetto VL, VanLe L, Bell J, Walker JL, Lee RB. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecologic Oncology*. 2000; 78(2):212–6. [PubMed: 10926805]
- Sall 1979 . Sall S, DiSaia P, Morrow CP, Mortel R, Prem K, Thigpen T, et al. A comparison of medroxyprogesterone serum concentrations by the oral or intramuscular route in patients with persistent or recurrent endometrial carcinoma. *American Journal of Obstetrics and Gynecology*. 1979; 135(5):647–50. [PubMed: 507117]

- Santin 2004 . Santin AD, Bellone S, O'Brien TJ, Pecorelli S, Cannon MJ, Roman JJ. Current treatment options for endometrial cancer. *Expert Review of Anticancer Therapy*. 2004; 4(4):679–89. [PubMed: 15270671]
- Sears 1994 . Sears JD, Greven KM, Hoen HM, Randall ME. Prognostic factors and treatment outcome for patients with locally recurrent endometrial cancer. *Cancer*. 1994; 74(4):1303–8. [PubMed: 8055452]
- Sehouli 2008 . Sehouli J, Koensgen D, Oskay-Ozelik G, Mustea A. New aspects of adjuvant therapy in endometrial cancer: current standards and future directions. *Critical Reviews in Oncology/Hematology*. 2008; 67(3):204–12. [PubMed: 18407513]
- Singh 2007 . Singh M, Zaino RJ, Filiaci VJ, Leslie KK. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group Study. *Gynecologic Oncology*. 2007; 106(2):325–33. [PubMed: 17532033]
- Slavik 1984 . Slavik M, Petty WM, Blessing JA, Creasman WT, Homesley HD. Phase II clinical study of tamoxifen in advanced endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Cancer Treatment Reports*. 1984; 68(5):809–11. [PubMed: 6722836]
- Sohaib 2007 . Sohaib SA, Houghton SL, Meroni R, Rockall AG, Blake P, Reznik RH. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. *Clinical Radiology*. 2007; 62:28–34. [PubMed: 17145260]
- Swenerton 1979 . Swenerton KD. Treatment of advanced endometrial carcinoma with tamoxifen. *New England Journal of Medicine*. 1979; 301(2):105. [PubMed: 449932]
- Temkin 2009 . Temkin SM, Fleming G. Current treatment of metastatic endometrial cancer. *Cancer Control*. 2009; 16(1):38–45. [PubMed: 19078928]
- Thigpen 1999 . Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *Journal of Clinical Oncology*. 1999; 17(6):1736–44. [PubMed: 10561210]
- Thigpen 2001 . Thigpen T, Brady MF, Homesley HD, Soper JT, Bell J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Journal of Clinical Oncology*. 2001; 19(2):364–7. [PubMed: 11208827]
- Whitney 2004 . Whitney CW, Brunetto VL, Zaino RJ, Lentz SS, Sorosky J, Armstrong DK. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecologic Oncology*. 2004; 92(1):4–9. [PubMed: 14751130]

PLAIN LANGUAGE SUMMARY

The effect of hormonal treatment on advanced or recurrent endometrial cancer

Endometrial cancer is cancer arising from the lining of the womb. Most women with endometrial cancer are diagnosed when their tumour is still confined to the body of the womb. However, about 10% of women with endometrial cancer are diagnosed when the disease is already at an advanced stage. The latter group of patients tend to have much poorer survival.

Treatment of women with advanced or recurrent endometrial cancer is challenging because often they suffer from other diseases and aggressive chemotherapy with or without surgery may not be beneficial or may even be harmful. Hormonal therapy in these cases is thought to be easily administered and to cause fewer side effects than systemic chemotherapy (standard treatment).

The purpose of this review was to assess the available literature on the effect of hormonal treatment on the survival of patients with advanced or recurrent endometrial cancer. We found six randomised controlled trials (RCTs) that assessed hormonal treatment in various forms and combinations in 542 eligible patients. We found insufficient evidence to suggest that hormonal therapy improves survival in these patients.

The main limitations of the review were the small number of patients included in the RCTs, the diversity of both the patient population and the hormonal agents used and the fact that quality of life was not reported in any of the trials. The quality of life with treatment is especially important for a condition that has a poor survival rate.

Figure 1.
Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Accurate classifications of outcomes?
Ayoub 1988	+	?	?	+	?	?	+
Pandya 2001	?	+	?	+	?	?	+
Rendina 1984	+	-	?	+	?	?	+
Stolyarova 2001	?	?	?	+	?	?	?
Thigpen 1999	+	?	?	+	?	?	+
Urbanski 1993	?	?	?	+	?	?	?

Figure 2.

Methodological quality summary: review authors' judgements about each methodological quality item for each included study.