Hormone therapy for endometriosis and surgical menopause

(Review)

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Hormone therapy for endometriosis and surgical menopause

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\textbf{ABSTRACT}

\textbf{Background}

Endometriosis is characterized by the presence of ectopic endometrial tissue that might lead to many distressing and debilitating symptoms. Despite available studies supporting standard hormone therapy for women with endometriosis and post-surgical menopause, there is still a concern that estrogens may induce a recurrence of the disease and its symptoms.

\textbf{Objectives}

This review aimed to look at pain and disease recurrence in women with endometriosis who used hormone therapy for post-surgical menopause.

\textbf{Search strategy}

We searched the Cochrane Menstrual Disorders and Subfertility Group Specialized Register (March 2008), Cochrane Central Register of Controlled Trials (CENTRAL) (\textit{The Cochrane Library} 2008, Issue 3), MEDLINE (1966 to March 2008), EMBASE (1980 to March 2008), and references lists of articles. Relevant journals and conference proceedings were handsearched.

\textbf{Selection criteria}

Randomized controlled trials studying hormone therapy for women with endometriosis in post-surgical menopause.

\textbf{Data collection and analysis}

Review authors assessed the eligibility of trials and their quality.

\textbf{Main results}

Two studies fulfilled our inclusion criteria. One trial compared the nonstop transdermal application of $17\beta$-estradiol (0.05 mg/day) combined with cyclic medroxy progesterone acetate (10 mg per day) for 12 days per month in women with a conserved uterus with nonstop tibolone (2.5 mg/day). The second trial used sequential administration of estrogens and progesterone with two 22 cm$^2$ patches applied weekly to produce a controlled release of 0.05 mg/day. Micronized progesterone was administered orally (200 mg/day) for 14 days with a 16-day interval free of treatment.

Pain and dyspareunia
The first trial reported recurrence of pain in the estrogen and progesterone arm in 4/10 of women compared with 1/11 in the tibolone arm. In the latter, 4/115 women reported recurrence of pain in the treatment group compared with 0/57 patients in the no-treatment arm. Neither finding was statistically different.

Confirmed recurrence or exacerbation of endometriosis

This outcome was not reported in the first trial. The second found that 2/115 of the treatment group developed recurrence of endometriosis with no recurrence reported in the no-treatment group. This was not statistically significant. No woman was re-operated on in the no-treatment group compared with 2/115 in the treatment group.

Authors’ conclusions

Hormone replacement therapy for women with endometriosis in post-surgical menopause could result in pain and disease recurrence. However, the evidence in the literature is not strong enough to suggest depriving severely symptomatic patients from this treatment. There is a need for more randomised controlled studies.

PLAIN LANGUAGE SUMMARY

Hormone therapy for women with endometriosis and surgical menopause

Endometriosis is known to result in variable severity of symptoms. For some women bilateral removal of the ovaries (oophorectomy) with or without an hysterectomy may be required to manage symptoms. This brings women into premature menopause. It is thought that hormone replacement therapy may enhance the recurrence of the disease due to its effect on the remaining endometriotic deposits in the pelvis. Only two small randomised controlled were identified in the literature that looked at this problem. Further research is required to clarify the effect of different hormone replacement therapy types on the recurrence of the disease and the associated pain including during sex.
BACKGROUND

Endometriosis is characterized by the presence of ectopic endometrial tissue that can lead to distressing and debilitating symptoms. The prevalence of endometriosis in the general population is not known but it has been estimated to affect about 7% of women of reproductive age (Haney 1991). Estimates of prevalence based upon visualization of the pelvic organs range from 1% to 50% (Chatman 1982; Sangi-Haghpeykar 1995).

There is considerable controversy regarding the optimal treatment of endometriosis. The choice of therapy usually depends upon the severity of symptoms, extent and location of the disease, desire for pregnancy, and a woman's age (Shaw 1992).

Endometriosis is generally believed to be an estrogen-dependent disorder. The many observations that support this view include amelioration of pre-existing endometriosis after surgical menopause (Kitawaki 2002) or natural menopause (Kitawaki 2002), and the growth of endometrial tissue in animals on estrogen therapy (Bruner-Tran 2002). This has led to the use of gonadotropin-releasing hormone agonists (GnRHa) to induce ovarian suppression, which is widely accepted as a treatment for endometriosis. The fall in estrogen levels following treatment with GnRHa leads to a significant improvement in the stage and symptoms of endometriosis (Donnez 1997; Fedele 2004). This may be used as a short-term strategy due to the risk of developing osteoporosis (Agarwal 2002).

Inducing menopause, either medically or surgically, has become one of the strategies for the management of the symptoms of endometriosis. Hysterectomy is commonly performed for endometriosis. Generally the ovaries are conserved in order to avoid the need for lengthy hormone replacement therapy. Removal of both ovaries is usually considered appropriate when the woman is approaching menopause or in the presence of extensive disease. Sometimes hysterectomy and bilateral salpingo-oophorectomy are inadequate if deep disease is left untreated (Donnez 1997; Fedele 2004; Matorras 2002).

Surgical and medical menopause are frequently associated with hypo-estrogenic side effects and changes in bone density, although these may resolve with treatment (Slavenon 1989). A number of studies have been conducted which investigated the effects of GnRHa ovarian suppression and progress of endometriosis (Cedars 1990; Makarainen 1996; Riis 1990; Surrey 1990). Others have investigated the effect of an add-back regimen that uses either estrogen or progestogens to avoid hot flushes (Cedars 1990; Riis 1990; Surrey 1992). Tibolone has also been evaluated, and shown to be effective, in a single small trial (Tabkin 1997). The results of this study showed that tibolone suppressed painful symptoms, vasomotor symptoms, and urinary markers of bone turnover.

Despite available evidence supporting standard hormone therapy for women with endometriosis post-surgical menopause (Lindsay 1996; Rock 1992), many gynaecologists remain concerned that estrogens may induce a recurrence of the disease and its symptoms. Several studies (Sagsaveen 2003) have been carried out to assess the effect of hormone therapy on hypo-estrogenic symptoms induced by GnRH analogues for women with endometriosis but only a few have addressed its effect on women experiencing post-surgical menopause.

The aim of this systematic review of published literature is to critically appraise the literature describing the risk of pain and disease recurrence among women who have had endometriosis and undergone bilateral salpingo-oophorectomy (BSO), with or without hysterectomy, and subsequently received hormone therapy.

OBJECTIVES

This review aimed to look at pain recurrence for women with endometriosis who used hormone therapy for post-surgical menopause.

METHODS

Criteria for considering studies for this review

Types of studies
All randomised controlled trials (RCTs) which studied women with endometriosis taking estrogen replacement therapy (ERT) or hormone replacement therapy (HRT) following surgical menopause.
Non-randomized and quasi-randomized controlled trials were excluded.

Types of participants
Inclusion criteria
Women with ectopic endometrial tissue that potentially could lead to distressing and debilitating symptoms regardless of the size and site of the deposits. Women who had undergone bilateral oophorectomy for treatment of endometriosis. Surgical menopause was defined as menopause due to surgical excision of both ovaries, with or without hysterectomy.
Exclusion criteria
Studies with participants who didn't fulfil the inclusion criteria were excluded.

Types of interventions

1. Estrogen versus placebo
2. Estrogen versus progestogen
3. Estrogen versus tibolone
4. Estrogen versus estrogen plus progestogen
5. Estrogen versus other hormones
We included all dosages, routes of administration, and frequency or duration of intervention.

Hormone therapy for endometriosis and surgical menopause (Review)
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Types of outcome measures

Primary outcome measures

- Pain and dyspareunia (painful intercourse)

The method of pain assessment was identified and, if possible, the participants were grouped into three major groups of: mild, moderate, or severe pain.

Secondary outcomes measures

- Confirmed recurrence or exacerbation of endometriosis (recurrence of disease symptoms that were suspected clinically and confirmed by tissue biopsy or ultrasound findings).
- Diagnosis of cancer (defined as the development of adenocarcinoma at the site of the endometriotic deposits).
- Mortality (death related directly or indirectly to the disease, its treatment, or both).
- Re-operation for endometriosis.

Search methods for identification of studies

We obtained relevant trials from the following sources (with the most recent search done on 18th March 2008).
1) We searched the Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL) (March 2008).
2) We searched MEDLINE using the optimally sensitive strategy for the identification of RCTs developed for The Cochrane Collaboration and a specific search strategy developed with input from the MDSG Trial Search Co-ordinators (Appendix 1).
3) We searched EMBASE using a search strategy adapted from that developed for The Cochrane Collaboration for the identification of RCTs and combined this with a specific search strategy developed with input from the MDSG Trial Search Co-ordinators (Appendix 5).
6) We also searched reference lists of standard Obstetrics and Gynaecology textbooks, review articles, and relevant trials.
7) We sent letters seeking information about unpublished or incomplete, ongoing trials to investigators known to be involved in previous trials.

Data collection and analysis

Selection of the studies

Four review authors (HK, AH, SH, HF) undertook study selection. We used the search strategy described above to obtain titles and abstracts of studies that may be relevant to the review. HK and AH independently screened the titles and abstracts of promising articles. They discarded studies that were not applicable and retained studies and reviews that might have included relevant data or information. HK and AH independently assessed retrieved abstracts and ordered the full texts of these studies when necessary. We did not require translation of any studies reported in non-English language journals. Where more than one publication of a trial existed, we included only the publication with the most complete data. We resolved any disagreements through discussion. No crossover trials were included.

SH and HF independently assessed the quality of studies to be included, without blinding to authorship or journal of publication, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The review authors resolved discrepancies by discussion with HK and AH (see Table 1).

1. Selection bias (randomization and allocation concealment)

We assigned a quality score for each trial using the following criteria.
A. Adequate concealment of allocation: telephone randomization, consecutively numbered sealed opaque envelopes.
B. Unclear whether adequate concealment of allocation: list or table used, sealed envelopes, study did not report on any concealment approach.
C. Inadequate concealment of allocation: open list of random number tables, use of case record numbers, dates of birth, or days of the week.

2. Performance bias (blinding of participants, researchers and outcome assessors)

We assessed blinding using the following criteria:
A. Blinding of participants (yes, no, or unclear);
B. Blinding of caregiver (yes, no, or unclear);
C. Blinding of outcome assessment (yes, no, or unclear).

3. Attrition bias (loss of participants, for example through withdrawals, dropouts, protocol deviations)

We assessed completeness of follow up using the following criteria:
A. less than 5% loss of participants;
B. 5% to 10% loss of participants;
C. more than 10% and less than 20% loss of participants;
D. more than 20% loss of participants.
We excluded all studies with more than 20% loss to follow up.

Analysis

For dichotomous outcomes (mortality, recurrence, cancer diagnosis, pain, dyspareunia, and re-operation) we expressed results as odds ratios (OR) with 95% confidence intervals (CI). No continuous data were reported hence weighted mean differences were not used.

We analysed data on an intention-to-treat basis. We included in the analysis all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention.
Heterogeneity
Heterogeneity was not tested as the two identified studies used different interventions.

Subgroup analysis
No subgroup analysis was possible from this data.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
HK and AH carried out data extraction independently using standard data extraction forms.
We intended to extract the following information from the two studies included in the review:
1. randomisation;
2. allocation concealment;
3. trial design multicentre or single centre, single phase or crossover;
4. number of patients randomised, excluded, and analysed;
5. duration, timing, and location of the trial;
6. source of funding;
7. type of surgical menopause;
8. type of intervention and control;
9. dose regime;
10. outcomes reported;
11. how outcomes were defined?
12. how outcomes were measured?
13. timing of outcome measurement.

Risk of bias in included studies
The quality of the two included studies (Fedele1999; Matorras2002) was adequate with a median Jadad score of 4 Figure 1. Figure 2
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?
Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

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<td>Matorras2002</td>
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Fedele et al (Fedele1999) used computer-generated randomization while for Matorras et al (Matorras2002) randomization was by means of sealed envelopes with allocation done by a person not connected to the study. Allocation concealment was unclear for Fedele et al (Fedele1999). In Fedele et al (Fedele1999) there was no blinding as the two interventions were different while for Matorras (Matorras2002) the gynaecologist performing the follow up was kept blinded to the method of intervention. In both studies there were no dropouts and all patients were accounted for. Neither of the two studies declared the funding or sponsorship source nor any conflict of interest.

Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Menstrual Disorders and Subfertility Group. Both trials were initially included in one analysis of hormone therapy for post-surgical menopause. Subgroup analysis was not possible as only two papers met the inclusion criteria. Results for each study were expressed as ORs with 95% CIs. Combined meta-analysis with RevMan software was not possible as the two studies used different interventions and controls, nor was statistical heterogeneity testing for the results of the two studies.

**Effects of interventions**

Two studies fulfilled our inclusion criteria for hormone replacement therapy in patients with endometriosis and post-surgical menopause (Fedele1999; Matorras2002). Fedele et al (Fedele1999) compared nonstop transdermal application of 17β-estradiol 0.05 mg/day combined with cyclic medroxy progesterone acetate 10 mg/day for 12 days/month with nonstop ti-bolone 2.5 mg/day in women with a conserved uterus. Matorras et al (Matorras2002) used sequential administration of estrogen and progesterone following Belchetz’s criteria (Belchetz 1994). Two 22 cm² patches were applied each week to produce a controlled release of 0.05 mg/day. Micronized progesterone was administered orally at a dose of 200 mg/day for 14 days with a 16-day interval free of treatment. This intervention arm was compared to the control group which did not receive treatment.

In Matorras et al (Matorras2002) the mean follow-up time was 45 months while Fedele et al (Fedele1999) followed up their participants for only 12 months. The main outcome studied by Matorras et al 2002 was recurrence of endometriosis diagnosed based on histological study, clinical findings, and ultrasound findings suggestive of endometriosis. Fedele et al (Fedele1999) used pain as the main outcome as reported by the participants at 3, 6, and 12-month follow-up visits after the start of the treatment.

**Pain and dyspareunia**

In Fedele et al (Fedele1999) the number of women who reported
recurrence of pain in the estrogen and progesterone arm was 4/10 compared with 1/11 in the tibolone arm. There was no significant difference between the two groups (OR 6.67, 95% CI 0.60 to 74.51). The wide CI reflects the small sample size in this study. In Matorras et al (Matorras2002) the number of patients who reported recurrence of pain was 4/115 in the estrogen with or without progesterone arm compared with 0/57 women in the no-treatment arm. The result was not significant (OR 4.64, 95% CI 0.25 to 87.71).

**Confirmed recurrence or exacerbation of endometriosis**

While this outcome was not reported in Fedele (Fedele1999), Matorras et al (Matorras2002) found that 2/115 of the estrogen with or without progesterone group developed recurrence of endometriosis that was confirmed histopathologically. No recurrence was reported in the no-treatment group. This finding was not statistically significant.

**Cancer diagnosis**

There was no documentation of cancer formation in either study (Fedele1999; Matorras2002).

**Re-operation for endometriosis**

In the Matorras study (Matorras2002) 2/115 women in the estrogen with or without progesterone group were re-operated on while no woman was re-operated in the no-treatment group. The OR was 2.53 (95% CI 0.12 to 53.64) and was not statistically significant.

**Mortality**

There was no case of mortality related to the medication reported in either study (Fedele1999; Matorras2002).

**Discussion**

This review addresses the controversial issue of the use of hormone replacement therapy for women with endometriosis and post-surgical menopause. There were only two randomised controlled studies that addressed this issue (Fedele1999; Matorras2002). Although they used similar inclusion criteria (women with endometriosis who underwent bilateral salpingoophorectomy with or without hysterectomy) the reviewed studies used different comparisons; meta-analysis was, therefore, not feasible.

Both studies have the potential for bias derived from the fact that Fedele et al (Fedele1999) did not apply blinding to the method of intervention and in Matorras (Matorras2002) only the gynaecologist following the women was kept unaware about the method of treatment. However, both studies had full retention of participants for the duration of follow up, with regular interim reviews as planned in the methodology. In the analysis, statistical heterogeneity was not tested as the studies used different control interventions. Neither study addressed development of cancer or mortality related to the disease after initiation of the treatment.

An assessment of pain recurrence after hormone replacement was difficult. In Fedele et al (Fedele1999) the pain recurrence was classified as either mild, moderate, or severe while in Matorras (Matorras2002) there was no such classification. This pain recurrence may be due to the underlying disease of endometriosis and the amount of residual tissue left after the initial surgery, which raises concerns. We considered the recurrence of pelvic pain and dyspareunia as signs of pain recurrence hence this review demonstrates the effect of hormone replacement therapy for women with endometriosis and post-surgical menopause on recurrence of dysmenorrhoea, dyspareunia, and non-menstrual pelvic pain when compared to tibolone and no treatment.

The recurrence rate of the endometriosis was assessed clinically and by pelvic ultrasonography in Matorras et al (Matorras2002). Both studies followed up the women for at least one year (mean of 45 months in Matorras et al (Matorras2002) and a minimum of 12 months in Fedele (Fedele1999)). There was no significant difference between the hormone replacement groups and the control groups in terms of pain recurrence for both studies. As there are only two studies addressing the issue of pain recurrence in women with endometriosis and post-surgical menopause, and both studies have used different control criteria, there is a possibility of publication bias.

In summary there is some evidence from two non-blinded randomised controlled trials that hormone replacement therapy for women with endometriosis and post-surgical menopause may lead to pain and disease recurrence.

**Authors’ Conclusions**

**Implications for practice**

Hormone replacement therapy for women with endometriosis and post-surgical menopause could result in pain and disease recurrence. However, the evidence in the literature is not strong enough to suggest depriving severely symptomatic patients from this treatment in order to relieve their menopausal symptoms.

There is a need for double-blinded randomised controlled studies to investigate further the effects of hormone replacement therapy on disease and pain recurrence.

**Implications for research**

Further studies are required to compare the use of different types of hormone replacement therapy in women with endometriosis and post surgical menopause. These studies need to address:
1. recurrence of the disease;  
2. recurrence of pain;  
3. women’s quality of life.

ACKNOWLEDGEMENTS

We would like to acknowledge National Guard Health Affairs; the Cochrane Menstrual Disorders and Subfertility Review Group; Riyadh, Kingdom of Saudi Arabia for their help and support during the preparation of this review.

REFERENCES

References to studies included in this review

Fedele 1999 (published data only)

Matorras 2002 (published data only)
Matorras R, Elorriaga MA, Pijoan JI, Ramon O, Rodriguez-Escudero FJ. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. *Fertility and Sterility* 2002;77(2):303–8.

References to studies excluded from this review

Alexander 2004 (published data only)

Arunugam 1998 (published data only)

Attar 2006 (published data only)

Bain 2006 (published data only)

Barrett-Connor 2005 (published data only)

Beard 1991 (published data only)

Bianchi 1997 (published data only)

Bradshaw 2002 (published data only)

Bulun 2005 (published data only)

Chalas 2005 (published data only)

Colau 2007 (published data only)

Davis 2003 (published data only)

Dennerstein 1980 (published data only)

Dowsett 2005 (published data only)
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Published online: 2009 Oct 28. doi: 10.1002/14651858.CD007426.pub2


Holub 2000 [published data only]

Holub 2001 [published data only]

Hansen 2006 [published data only]

Goulding 1991 [published data only]

Graziottin 2007 [published data only]

Frackiewicz 2003 [published data only]

Friedlander 2002 [published data only]

Ghezzi 2005 [published data only]

Fedele 2005 [published data only]

Farquhar 2006 [published data only]

Farquhar 2006 [published data only]

Johnson 2006 [published data only]
Johnson 2006 [published data only]

Jones 2002 [published data only]

Kouides 2006 [published data only]

Kroon 2005 [published data only]

Kuenzel 2006 [published data only]

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Lalchandani 2005 [published data only]

Leyendecker 2002 [published data only]

Lobo 1984 [published data only]

Loizzi 2005 [published data only]

Long 2006 [published data only]

Lopez-Olmos 2003 [published data only]

Lu 1995 [published data only]

Luciano 2006 [published data only]

Mannix 2004 [published data only]

Mendoza 2000 [published data only]

Mizutani 1995 [published data only]

Modugno 2003 [published data only]

Moen 2002 [published data only]

Morini 1993 [published data only]

Mousa 2007 [published data only]

Murphy 1995 [published data only]

Nagao 2006 [published data only]

Nagata 2001 [published data only]

Namnoum 1995 [published data only]

Nappi 2006 [published data only]

Nasir 2004 [published data only]

Noble 1979 [published data only]

Ozawa 2006 [published data only]

Ozols 2004 [published data only]

Perry 1996 [published data only]
Setnikar 1997  [published data only]


Tan 2008  [published data only]


Tietjen 2006  [published data only]


Tok 2006  [published data only]


Uemura 2000  [published data only]


Usman 2008  [published data only]


Varma 2006  [published data only]


Velasco 2006  [published data only]


Vercellini 2008  [published data only]


Walker 2005  [published data only]


Weiss 1982  [published data only]


Winkel 2001  [published data only]


Wolff 1982  [published data only]


Piltonen 2002  [published data only]


Pruthi 2007  [published data only]


Purdie 1999  [published data only]


Rattanachaiyanont 03  [published data only]


Rees 2006  [published data only]


Reid 1996  [published data only]


Robson 2003  [published data only]


Roman 2007  [published data only]


Rotella 2006  [published data only]


Santos Gonzalez 2001  [published data only]


Schor 1999  [published data only]


Schwenkhagen 2006  [published data only]


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Additional references

Agarwal 2002


Belchetz 1994


Bruner-Tran 2002


Cedars 1990


Chatman 1982


Donnez 1997


Fedele 2004


Haney 1991


Kitawaki 2002


Lindsay 1996


Makarainen 1996


Matorras 2002

Matorras R, Elerriega MA, Pijoan JI, Ramon O. Recurrence of endometriosis in women with bilateral adnexectomy (with or without total hysterectomy) who received hormone replacement therapy. *Fertility and Sterility* 2002;77(2):303–8.

Riis 1990


Rock 1992


Sagsveen 2003


Sangi-Haghpeykar 1999


Shaw 1992


Slenvenson 1989


Surrey 1990


Surrey 1992


Takkin 1997


* Indicates the major publication for the study
Characteristics of included studies  [ordered by study ID]

Fedele1999

| Methods | RCT  
| Computer-generated randomization. |
| Participants | Symptomatic patients with deeply infiltrating endometriotic nodules that recurred after one or more previous operations. Patients had bilateral oophorectomy with or without hysterectomy. The disease was not completely eradicated after the surgery. |
| Interventions | Nonstop transdermal 17β-estradiol 0.05 mg/d combined with cyclic medroxy progesterone acetate 10 mg/d for 12 days/month in women with conserved uterus  
| Control: nonstop tibolone 2.5 mg/d. |
| Outcomes | Pain as reported by the patients at 3, 6, and 12 months after the start of the treatment. |
| Notes | The duration of the treatment was at least 12 months.  
| All women were followed for 12 months and no participant suspended the therapy which indicates that intention to treat analysis was applied.  
| There was no blinding as the method of intervention and the control were different. |

Risk of bias

| Item | Authors’ judgement | Description |
| Adequate sequence generation? | Yes | Randomization was computer generated |
| Allocation concealment? | Unclear | Unclear, the method was not mentioned |
| Blinding? | No | The intervention and control were different |
| Incomplete outcome data addressed? | Yes | The reported outcome was clear: pain as reported by the patient at 3, 6, and 12 months after the start of the treatment |
| Free of selective reporting? | Yes | The reported outcome was clear and as planned in the methodology |
| Free of other bias? | Yes | Apart from blinding’s and allocation concealment, there was no other bias |
### Methods

RCT

The randomization was done using sealed envelopes. The randomization was done by a person not connected to the study.

### Participants

Women with histological diagnosis of endometriosis in whom BSO was done irrespective of associated surgical procedures. No hormonal treatment during 6-month period before surgery. No medical treatment of endometriosis.

### Interventions

Sequential administration of estrogen and progesterone following Belchetz's criteria. Two 22 cm² patches were applied per week which produced a controlled release of 50 microgram/day. Micronized progesterone was administered orally during 14 days, 200 mg/24 hours, with a 16-day interval free of treatment.

### Outcomes

Recurrence of endometriosis that was diagnosed based on histological study, clinical findings, and ultrasound findings suggestive of endometriosis.

### Notes

There was no placebo but the women were all monitored by the same gynaecologist who was kept unaware of their treatment status.

### Risk of bias

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<td>Yes</td>
<td>The randomization was done using sealed envelopes</td>
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<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Adequate, randomization was done by a person not related to the study</td>
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<td>Blinding?</td>
<td>No</td>
<td>There was no blinding except for the assessing gynaecologist who was kept unaware of treatment status</td>
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<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>There was a clearly addressed outcome: recurrence of endometriosis that was diagnosed based on histological study, clinical findings, and ultrasound findings suggestive of endometriosis</td>
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<td>Free of selective reporting?</td>
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<td>Free of other bias?</td>
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### Characteristics of excluded studies [ordered by study ID]

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## DATA AND ANALYSES

### Comparison 1. Estrogen with or without progesterone versus placebo or no treatment

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<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>1 Number of patients reporting pain</td>
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<td>172</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>4.64 [0.25, 87.71]</td>
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<td>2 Recurrence confirmed by histopathology</td>
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<td>3 Re-operation</td>
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### Comparison 2. Estrogen with or without progesterone versus tibolone

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<th>No. of participants</th>
<th>Statistical method</th>
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<tr>
<td>1 Number of patients reporting pain</td>
<td>1</td>
<td>21</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>6.67 [0.60, 74.51]</td>
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### Analysis 1.1. Comparison 1 Estrogen with or without progesterone versus placebo or no treatment, Outcome: 1 Number of patients reporting pain.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 1 Estrogen with or without progesterone versus placebo or no treatment

Outcome: 1 Number of patients reporting pain

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Estrogen +/- prog n/N</th>
<th>Placebo or no treat n/N</th>
<th>Odds Ratio M-H (Fixed, 95% CI)</th>
<th>Weight</th>
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<tr>
<td>Matorras2002</td>
<td>4/115</td>
<td>0/57</td>
<td>100.0 %</td>
<td>4.64</td>
<td>4.64 [0.25, 87.71]</td>
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<tr>
<td>Total (95% CI)</td>
<td>115</td>
<td>57</td>
<td>100.0 %</td>
<td>4.64</td>
<td>4.64 [0.25, 87.71]</td>
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Total events: 4 (Estrogen +/- prog), 0 (Placebo or no treat)

Heterogeneity: not applicable

Test for overall effect: Z = 1.02 (P = 0.31)
### Analysis 1.2. Comparison 1 Estrogen with or without progesterone versus placebo or no treatment, Outcome 2 Recurrence confirmed by histopathology.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 1 Estrogen with or without progesterone versus placebo or no treatment

Outcome: 2 Recurrence confirmed by histopathology

<table>
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<th>Study or subgroup</th>
<th>Estrogen +/- prog</th>
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<th>Odds Ratio M-H,Fixed 95% CI</th>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>115</strong></td>
<td><strong>57</strong></td>
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<td>100.0%</td>
<td><strong>2.53 [0.12, 53.64]</strong></td>
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Total events: 2 (Estrogen +/- prog), 0 (Placebo/no treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.60 (P = 0.55)

### Analysis 1.3. Comparison 1 Estrogen with or without progesterone versus placebo or no treatment, Outcome 3 Re-operation.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 1 Estrogen with or without progesterone versus placebo or no treatment

Outcome: 3 Re-operation

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<th>Study or subgroup</th>
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<td><strong>Total (95% CI)</strong></td>
<td><strong>115</strong></td>
<td><strong>57</strong></td>
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<td><strong>2.53 [0.12, 53.64]</strong></td>
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Total events: 2 (Estrogen +/- prog), 0 (Placebo/no treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.60 (P = 0.55)
Analysis 2.1. Comparison of Estrogen with or without progestosterone versus tibolone, Outcome 1 Number of patients reporting pain.

Review: Hormone therapy for endometriosis and surgical menopause

Comparison: 2 Estrogen with or without progestosterone versus tibolone

Outcome: 1 Number of patients reporting pain

<table>
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<th>Study or subgroup</th>
<th>Estrogen +/- prog</th>
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<td>Fedele1999</td>
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<td>Total (95% CI)</td>
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<td>11</td>
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Total events: 4 (Estrogen +/- prog), 1 (Tibolone)
Heterogeneity: not applicable
Test for overall effect: Z = 1.54 (P = 0.12)

A P P E N D I C E S

Appendix 1. MEDLINE

MEDLINE search strategy (1950 to 18 March 2008)
1 exp Endometriosis/ (12393)
2 Endometriosis.tw. (10555)
3 exp Pelvic Pain/ (4372)
4 (Pelvic adj2 Pain).tw. (3537)
5 Dyspareunia/ (938)
6 Dyschezia$.tw. (98)
7 Dyspareunia$.tw. (1433)
8 (pain$ adj2 bowel movement$).tw. (40)
9 exp Ovariectomy/ (15381)
10 Ovariectomy$.tw. (17565)
11 oophorect$.tw. (4897)
12 (remov$ adj2 ovar$).tw. (772)
13 (salpingo adj ovariec$).tw. (7)
14 (surgic$ adj3 menopause).tw. (504)
15 or/1-8 (20739)
16 or/9-14 (27561)
17 or/15-16 (626)
18 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (16022)
19 (Hormone adj2 therapeut$).tw. (15598)
20 HRT.tw. (5476)
21 Tibolone.tw. (640)
22 exp Estrogens/ (120957)
23 exp Progesterone/ (56827)
24 (Estrogen$ or Progest$).tw. (120763)
25 or/18-24 (210538)
26 or/17 and 25 (173)
Appendix 2. Psych INFO

1 exp Endometriosis/ (0)
2 Endometriosis.tw. (91)
3 exp Pelvic Pain/ (0)
4 (Pelvic adj2 Pain).tw. (248)
5 Dyspareunia/ (134)
6 Dyschezia$.tw. (3)
7 Dyspareunia$.tw. (267)
8 (pain$ adj2 bowel movement$).tw. (6)
9 exp Ovariectomy/ (1115)
10 Ovariectom$.tw. (2403)
11 oophorect$.tw. (108)
12 (remov$ adj2 ovar$).tw. (40)
13 (salpingo adj ovariectomy).tw. (0)
14 (surgic$ adj3 menopause).tw. (64)
15 or/1-8 (589)
16 or/9-14 (2634)
17 15 and 16 (3)
18 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (1056)
19 (Hormone adj2 therap$).tw. (971)
20 HRT.tw. (361)
21 Tibolone.tw. (18)
22 exp Estrogens/ (3495)
23 exp Progesterone/ (1390)
24 (Estrogen$ or Progest$).tw. (5595)
25 or/18-24 (7349)
26 17 and 25 (1)
Appendix 3. CINAHL

1 exp Endometriosis/ (566)
2 Endometriosis.tw. (463)
3 exp Pelvic Pain/ (775)
4 (Pelvic adj2 Pain).tw. (517)
5 Dyspareunia/ (150)
6 Dyschezia$.tw. (1)
7 Dyspareunia$.tw. (143)
8 (pain$ adj2 bowel movement$).tw. (5)
9 exp Ovariectomy/ (448)
10 Ovariectom$.tw. (145)
11 oophorect$.tw. (276)
12 (remov$ adj2 ovar$).tw. (20)
13 (salpingo adj ovariectomy).tw. (0)
14 (surgic$ adj3 menopause).tw. (76)
15 or/1-8 (1672)
16 or/9-14 (674)
17 15 and 16 (35)
18 exp hormone replacement therapy/ or exp estrogen replacement therapy/ (4517)
19 (Hormone adj2 therap$).tw. (2363)
20 HRT.tw. (1006)
21 Tibolone.tw. (57)
22 exp Estrogens/ (4247)
23 exp Progesterone/ (788)
24 (Estrogen$ or Progest$).tw. (3460)
25 estra$.tw. (790)
26 or/18-25 (9451)
27 17 and 26 (10)
28 exp clinical trials/ (57427)
29 Clinical trial.pt. (29998)
30 (clinical$ adj trial$1).tw. (13150)
31 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (7801)
32 Random?ed control$ trial$.tw. (11197)
33 Random assignment/ (17445)
34 Random$ allocat$.tw. (1211)
35 Placebo$.tw. (10846)
36 Placebos/ (4145)
37 Quantitative studies/ (3735)
38 Allocat$ random$.tw. (73)
39 or/28-38 (79254)
40 27 and 39 (2)
41 from 40 keep 1-2 (2)
Appendix 4. CENTRAL

1 exp Endometriosis/ (347)
2 Endometriosis.tw. (581)
3 Pelvis Pain Syndrome/ (0)
4 (Pelvic adj2 Pain).tw. (309)
5 Dyspareunia/ (43)
6 Dyspareunia$.tw. (133)
7 Dyschezia$.tw. (4)
8 (pain$ adj2 bowel movement$).tw. (13)
9 exp ovariectomy/ or exp salpingooophorectomy/ (190)
10 Ovariectom$.tw. (65)
11 salpingooophorectom$.tw. (1)
12 oophorect$tw. (293)
13 (remov$ adj2 ovar$).tw. (11)
14 (salpingo adj ovaricectomy).tw. (0)
15 (surgic$ adj3 menopause).tw. (76)
16 or/1-8 (954)
17 or/9-15 (472)
18 16 and 17 (20)
19 exp Hormone Substitution/ (0)
20 (Hormone adj2 therap$).tw. (2360)
21 (hormone adj3 substitut$).tw. (53)
22 HRT.tw. (1012)
23 exp Tibolone/ (0)
24 Tibolone.tw. (309)
25 exp Estrogen/ (3675)
26 exp Progesterone/ (1787)
27 tibolone.tw. (309)
28 (Estrogen$ or Progest$).tw. (5916)
29 estra$.tw. (3383)
30 or/19-29 (10176)
31 18 and 30 (8)
32 from 31 keep 1-8 (8)

Appendix 5. EMBASE

1 exp Endometriosis/ (10166)
2 Endometriosis.tw. (8803)
3 Pelvis Pain Syndrome/ (4221)
4 (Pelvic adj2 Pain).tw. (3474)
5 Dyspareunia/ (2069)
6 Dyspareunia$.tw. (1403)
7 Dyschezia$.tw. (79)
8 (pain$ adj2 bowel movement$).tw. (36)
9 exp ovariectomy/ or exp salpingooophorectomy/ (18093)
10 Ovariectom$.tw. (14109)
11 salpingooophorectom$.tw. (107)
12 oophorect$tw. (4363)
13 (remov$ adj2 ovar$).tw. (576)
14 (salpingo adj ovaricectomy).tw. (7)
15 (surgic$ adj3 menopause).tw. (481)
16 or/1-8 (16927)
17 or/9-15 (24421)
18 16 and 17 (830)
19 exp Hormone Substitution/ (25640)
20 (Hormone adj2 therap$).tw. (14911)
21 (hormone adj3 substitut$).tw. (640)
22 HRT.tw. (6186)
23 exp Tibolone/ (1638)
24 Tibolone.tw. (754)
25 exp Estrogen/ (117030)
26 exp Progesterone/ (37148)
27 tibolone.tw. (754)
28 (Estrogen$ or Progest$).tw. (95948)
29 extra$tw. (44850)
30 or/19-29 (183085)
31 18 and 30 (280)
32 Clinical trial/ (495185)
33 Randomized controlled trials/ (155511)
34 Random Allocation/ (25203)
35 Single-Blind Method/ (7410)
36 Double-Blind Method/ (68576)
37 Cross-Over Studies/ (20046)
38 Placebos/ (111054)
39 Randomi?ed controlled trial$.tw. (28060)
40 RCT.tw. (2194)
41 Random allocation.tw. (605)
42 Randomly allocated.tw. (9592)
43 Allocated randomly.tw. (1314)
44 (allocated adj2 random).tw. (552)
45 Single blind$.tw. (7066)
46 Double blind$.tw. (81296)
47 ((treble or triple) adj blind$).tw. (127)
48 Placebo$.tw. (104327)
49 Prospective Studies/ (73142)
50 or/32-49 (651841)
51 Case study/ (5369)
52 Case report.tw. (110903)
53 Abstract report/ or letter/ (461484)
54 or/51-53 (575754)
55 50 not 54 (629234)
56 animal/ (18235)
57 human/ (6058876)
58 56 not 57 (14465)
59 55 not 58 (629138)
60 31 and 59 (49)
61 from 60 keep 1-49 (49)
HISTORY

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CONTRIBUTIONS OF AUTHORS

Hanan Al Kadri (HK) and Ali Hajeer (AH) screened titles and abstracts independently. They discarded studies that were not applicable. HK and AH also independently assessed the retrieved abstracts and, when necessary, ordered the full texts of these studies to determine which study satisfied the inclusion criteria.

The same review authors also carried out data extraction independently. They resolved disagreements in consultation with the other two authors, Samar Hassan (SH) and Haya AlFozan (HF).

SH and HF independently assessed the quality of studies to be included. They resolved discrepancies by discussion with HK and AH. HK wrote the final manuscript and together with AH produced the final review.

DECLARATIONS OF INTEREST

We certify that we have no affiliations or involvement in any organization or entity with a direct financial interest in the subject matter of the review (from, for example, employment, consultancy, stock ownership or honoraria).

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