

# Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women (Review)

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[Intervention Review]

# Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

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## ABSTRACT

### Background

Pelvic organ prolapse is common and can be detected in up to 50% of parous women although many are asymptomatic. Oestrogen preparations are used to improve vaginal thinning (atrophy). It is possible that oestrogens, alone or in conjunction with other interventions, might prevent or assist in the management of pelvic organ prolapse, for example by improving the strength of weakened supporting structures.

### Objectives

To determine the effects of oestrogens or drugs with oestrogenic effects alone, or in conjunction with other treatments, both for prevention and treatment of pelvic organ prolapse.

### Search strategy

We searched the Cochrane Incontinence Group Specialised Register of trials (searched 6 May 2010), MEDLINE (January 1950 to April 2010) as well as reference lists of relevant articles.

### Selection criteria

Randomised or quasi-randomised controlled trials that included the use of any oestrogens or drugs with oestrogenic (or anti-oestrogenic) actions for pelvic organ prolapse.

### Data collection and analysis

Trials were assessed and data extracted independently by two review authors.

### Main results

Three trials and one meta-analysis of adverse effects of a further three trials were identified. One trial did not provide useable data. Two trials included 148 women with prolapse, one included 58 postmenopausal women and the meta-analysis reported a mixed population (women with and without prolapse) of postmenopausal women (N=6984). The meta analysis and one other small trial investigated the effect of selective oestrogen receptor modulators (SERMs) for treatment or prevention of osteoporosis but also collected data of the

effects on prolapse. Interventions included oestradiol, conjugated equine oestrogen and two (SERMs), raloxifene and tamoxifen. Only one small trial addressed the primary outcome (prolapse symptoms).

One small treatment trial of oestradiol for three weeks before prolapse surgery found a reduced incidence of cystitis in the first four weeks after surgery but this unexpected finding needs to be confirmed in a larger trial.

A meta-analysis of adverse effects of a SERM, raloxifene (used for treatment or prevention of osteoporosis in postmenopausal women) found a statistically significant reduction in the need for prolapse surgery at three year follow up (OR 0.50, 95% CI 0.31 to 0.81), but this was statistically significant only in women older than 60 years (OR 0.68, 95% CI 0.22 to 2.08) and the total number of women having prolapse surgery was small. A further small trial comparing conjugated equine oestrogen, raloxifene, tamoxifen and placebo in postmenopausal women having pelvic floor muscle training was too small to detect effects on prolapse outcomes.

### Authors' conclusions

There was limited evidence from randomised controlled trials regarding the use of oestrogens for the prevention and management of pelvic organ prolapse. The use of local oestrogen in conjunction with pelvic floor muscle training before surgery may reduce the incidence of post-operative cystitis within four weeks after surgery. Oral raloxifene may reduce the need for pelvic organ prolapse surgery in women older than 60 years although this cannot be taken as an indication for practice.

There is a need for rigorous randomised controlled trials with long term follow up to assess oestrogen preparations for prevention and management of pelvic organ prolapse, particularly as an adjunctive treatment for women using pessaries and also before and after prolapse surgery.

## PLAIN LANGUAGE SUMMARY

### Oestrogens for treatment or prevention of pelvic organ prolapse in women

Many women suffer from pelvic organ prolapse, which is a downward descent of the vagina (front passage) and/or uterus (womb). It is more common after childbirth and after the menopause. Women may not have symptoms or they may feel bulge and/or pressure vaginally, as well as a range of urinary, bowel and sexual problems. These symptoms may affect quality of life. Prolapse is associated with weakness in muscles and supporting structures in the pelvis. Treatment can be conservative (pessaries or rings), pelvic floor muscle training or surgery. Oestrogen (female hormone) treatment can be used to reduce thinning of the vaginal and pelvic tissues. This may help to reduce or prevent the symptoms of prolapse, or may be used to make other prolapse treatments work better. This review did not find any clear evidence to suggest whether oestrogens work. However, as they are often used, especially with pessaries or before and after prolapse surgery, research is needed to identify any benefits or risks.

## BACKGROUND

### Risk factors

### Description of the condition

The International Continence Society defines pelvic organ prolapse (POP) as downward descent of the pelvic organs, which results in a protrusion of the vagina and/or uterine cervix and does not include rectal prolapse (Abrams 2002). Up to 50% of women who have given birth to at least one child (parous women) may have a prolapse (DeLancey 1993). Around 10% of women have prolapse or incontinence surgery in their lifetimes (Olsen 1997).

A number of risk factors for POP have been identified. These include age and ethnic origin (Hendrix 2002; Scherf 2002), menopause, number of births (parity) (Tegerstedt 2005), vaginal delivery (Lukacz 2006), increased intra-abdominal pressure as a result of bowel dysfunction (Spence-Jones 1994), manual work (Woodman 2006), and obesity (Bradley 2007), as well as inherent weakness of supporting connective tissues such as that encountered in those with joint hyper-mobility or genetic conditions such as Marfan's or Ehlers Danlos syndrome (Carley 2000).

## Symptoms of prolapse

Many women may have a prolapse without any symptoms. If symptomatic, the condition may present with sense of pressure or bulge vaginally in association with a variety of urinary, bowel (Bradley 2005; Ghetti 2005), and sexual symptoms (Digesu 2005), as well as lower abdominal pain, backache and perineal discomfort (Bonetti 2004). There is also a considerable impact on quality of life and body image (Jelovsek 2006).

## Description of the intervention

Management choices for women with POP include conservative and surgical measures (Maher 2010). Conservative measures, such as pelvic floor muscle training (PFMT) (Hagen 2006) and mechanical devices (Adams 2004), are usually reserved for women who are frail or have a mild prolapse, those who decline surgery, and those who wish to have more children. The role of pelvic floor muscle training is unproven, but, in theory, could support the prolapse by increasing the tone and strength of the pelvic floor muscles. Mechanical devices may be effective, but need to be changed regularly and can cause discharge, bleeding and ulceration. Surgical methods include anterior and posterior vaginal wall repair, with or without cervical amputation or vaginal hysterectomy, and sacrospinous fixation or sacrocolpopexy for apical prolapse (Maher 2010). Surgery, as for any operation, is associated with risks (anaesthetic, thrombosis, cardiovascular), and has a 30% failure rate (Olsen 1997).

Oestrogens (but not SERMs) are often used in conjunction with these treatments in the hope of enhancing their effects in improving prolapse symptoms. Oestrogens are also used on their own, to treat specific prolapse symptoms such as vaginal thinning (atrophy), dryness and resulting discomfort and pain with intercourse, which are all made worse when the vaginal skin overlying the prolapse is exposed outside the vulva. However, there is no information about how often oestrogens are used in any of these circumstances or whether they work.

There is also a group of selective oestrogen receptor modulators (SERMs, such as raloxifene and tamoxifen), which have a selective effect on oestrogen receptors in different organs (Silfen 1999; Shelly 2008). They produce oestrogen-like actions in some tissues (agonist) and oestrogen-blocking actions (antagonist) in others (Silfen 1999). However, they are not usually used actively to treat prolapse or prolapse symptoms in the same way that oestrogenic preparations are, but they can be used for osteoporosis. They are included in this review because of their mechanism of action (on oestrogen receptors), which may also affect prolapse.

Individual SERMs may have different effects on different types of tissue. These patterns of action suggest that each clinical endpoint (such as effects on prolapse, incontinence, and breast, bone and endometrium tissue) must be evaluated individually. Conclusions about any particular SERM can only be established through appropriate clinical trials (Shelly 2008).

Oestrogens and drugs with oestrogenic effects (such as SERMs) are also used to prevent and treat osteoporosis by increasing the density (thickness) of the bone in postmenopausal women.

Adverse effects of oestrogens or SERMs can include thromboembolism, endometrial cancer (lining of the womb, prevented by giving progestogens periodically), cardiovascular problems such as heart attacks or stroke, vaginal bleeding and breast cancer, but these risks are less when they are used locally (Suckling 2006).

## Types of oestrogen preparations

Both natural and synthetic oestrogens have been used for hormone replacement therapy (Prifti 2003), though synthetic oestrogens have a greater metabolic impact (Van Campenhout 1980):

- Natural oestrogens include oestradiol, oestrone, oestriol and conjugated oestrogens (Helgason 1982).
- Synthetic oestrogens include ethinyl oestradiol and mestranol (Van Campenhout 1980).
- SERMs

## Routes and choice of oestrogen administration

Oestrogens can be given so that they are absorbed throughout the body, i.e. systemically (Rad 2006), or in a limited area, i.e. locally (Manonai 2006).

Systemic use includes:

- oral delivery (MacLennan 2004);
- transdermal skin patches or gel (Samsioe 2007; Suvanto 1998); or
- subcutaneous implants (Horner 2006).

Local use includes:

- vaginal cream (Long 2006);
- vaginal tablets (Eriksen 1992); or
- a vaginal ring impregnated with an oestrogen (Casper 1999).

Transdermal and subcutaneous administration avoids the gut and first-pass effect on the liver, which means that lower doses can be used (Stevenson 1996). With subcutaneous implants, administration is less frequent (every six months (Suhonen 1993)), but there is the risk of tachyphylaxis (initial high levels which then reduce over time in an uncontrollable way (Buckler 1995)), or endometrial stimulation may continue after stopping treatment (Gangar 1990). Use of local oestrogen results in less systemic absorption, which may reduce the incidence of systemic side effects (Lethaby 2007; Mainini 2005).

For all women who take oestrogens, the use of progestogens must be considered if the uterus is still present, because of the risk of endometrial hyperplasia (thickening of the cells of the endometrium that may lead to atypical cells that can cause carcinoma) (Lethaby 2007). The risk may be less with local administration (Suckling 2006), or with intermittent administration (i.e. successive short term courses as required for symptoms).

Selective oestrogen receptor modulators, on the other hand, are given only orally (Shelly 2008).

## How the intervention might work

### The role of oestrogen in relation to pelvic organ prolapse

The female genital tract is sensitive to oestrogen. Lack of oestrogen after the menopause leads to atrophy with symptoms such as vaginal dryness or painful/difficult sexual intercourse (dyspareunia) (Xu 2005). Loss of vaginal folds or creases (rugae) is a recognised feature of the lack of oestrogen (Whiteside 2005). Oestrogen hormone replacement therapy has been used to treat it (Van Voorhis 2005).

Prolapse can be associated with weakening or thinning (atrophy) of the genital tract tissues (Delancey 2002). It is possible that oestrogen deficiency weakens the supporting ligaments of the pelvic organs (Reay 2003), the pelvic floor muscles and the pelvic fascia, as well as thinning the vaginal mucous membrane (mucosa). There are fewer oestrogen receptors and the pelvic ligaments become weaker and thinner with every year after the menopause (Lang 2003). These factors could contribute to prolapse.

It is possible, therefore, that oestrogens or drugs such as SERMs with oestrogen-like actions, alone or in conjunction with other forms of management, may help the treatment of pelvic organ prolapse by improving the strength of weakened supporting ligaments, muscles and vaginal mucosa. The evidence, however, from laboratory studies of oestrogen receptors in tissues is conflicting (Copas 2001).

### Rationale for use of oestrogen in women with pelvic organ prolapse

The aims of oestrogen treatment in the management of pelvic organ prolapse are to:

- restore the thickness, elasticity and moistness of the vaginal wall;
- restore the vaginal pH;
- improve the strength and function of the pelvic fascia and ligaments that support the pelvic organs;
- improve the strength and function of the pelvic floor muscles.

Biologically, it is plausible that if oestrogens have these effects, they might prevent, delay the onset of, or treat prolapse or its symptoms. It might also improve the effectiveness of other treatments, such as mechanical devices (Adams 2004), PFMT (Hagen 2006) or surgery (Maher 2010). However, these Cochrane reviews have shown, to date, that:

- there are no trials assessing the value of oestrogens, local or systemic, in conjunction with PFMT, to treat pelvic organ prolapse (Hagen 2006);
- local oestrogen treatment has been used in conjunction with pessaries (plastic vaginal devices that keep the vagina and/or uterus in position) (Poma 1981), though there is no evidence from RCTs about whether it reduces the incidence of bleeding, discharge, ulceration, or the need for pessary replacement (Adams 2004);
- local oestrogens have been used to strengthen vaginal tissue prior to prolapse surgery, but there is no evidence to show whether or not this is beneficial (e.g. by reducing tearing and bleeding during surgery, avoiding the need for blood transfusion, improving tissue healing and/or facilitating and hastening post-operative recovery) (Maher 2010).

The potential benefits of oestrogen treatment must be balanced against the risk of adverse effects such as thromboembolic disease, coronary heart disease, cerebrovascular accident, uterine hyperplasia or cancer, breast cancer, or gall bladder disease. The effect of oestrogen on the endometrium has been studied extensively, especially in relation to its use in hormone replacement therapy. Prolonged exposure to unopposed oestrogen without progestogen is known to cause endometrial hyperplasia and risk the development of endometrial carcinoma (Persson 1999).

The effect of selective oestrogen receptor modulators (SERMs) on the endometrium has been under investigation. For example, tamoxifen can lead to increased endometrial thickness, endometrial polyps and endometrial hyperplasia (Chalas 2005) as well as endometrial carcinoma. On the other hand, raloxifene reduces the incidence of endometrial cancer (DeMichele 2008). However, their effect in relation to pelvic organ prolapse has not been clarified (Shelly 2008).

### Why it is important to do this review

Oestrogens are being used in clinical practice to treat women with pelvic organ prolapse, often as adjuncts to improve the prolapse outcomes from other treatments such as surgery or pessaries. However, there is no evidence to support this practice. This review examined randomised controlled trials looking at such use, to provide evidence to guide appropriate patient management and identify gaps in the evidence which require future research.

## OBJECTIVES

To determine the effects of oestrogen / SERM treatment alone, or in conjunction with other treatments, as

- (A) Treatment, or
- (B) Prevention of pelvic organ prolapse.

The following comparisons were made:

1. Oestrogen / SERM treatment alone versus no treatment/ placebo;
2. Oestrogen / SERM treatment alone versus another treatment;
3. Oestrogen / SERM treatment in conjunction with physical treatment (e.g. pelvic floor muscle training) versus physical treatment alone;
4. Oestrogen / SERM treatment in conjunction with the use of vaginal pessaries versus the use of vaginal pessaries alone;
5. Oestrogen / SERM treatment in conjunction with surgery versus surgery alone.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised or quasi-randomised controlled trials, with an oestrogen or SERM in at least one arm of the trial.

#### Types of participants

Two populations were considered.

A) Postmenopausal adult women with any degree of pelvic organ prolapse, regardless of symptoms.

Pelvic organ prolapse included one or more of the following:

- Anterior vaginal wall prolapse (cystocele, urethrocele);
- Posterior vaginal wall prolapse (rectocele, enterocele);
- Prolapse of the upper vagina (cervical or uterine prolapse, vault prolapse).

B) Postmenopausal women without symptomatic pelvic organ prolapse using oestrogens or SERMs (to treat another condition e.g. osteoporosis) or to prevent the development or deterioration of pelvic organ prolapse.

#### Types of interventions

The use of any pharmaceutical form of oestrogens or SERMs by any route and in any dose, as used by trialists, including:

Systemic administration via:

- oral tablets;
- transdermal patches;
- transdermal gels;
- subcutaneous implants.

Local application via:

- vaginal cream;
- vaginal tablets;
- vaginal rings.

Duration of treatment, including the need for repeated courses of treatment, was as reported by trialists.

Comparator interventions included placebo, conservative (e.g. lifestyle, pelvic floor muscle training), pessaries or surgery alone, or in combination with oestrogens. The addition of progesterone to protect against endometrial cancer was accepted when necessary as part of oestrogen treatment as reported by the trialists.

### Types of outcome measures

#### Primary outcomes

Primary outcomes of treatment trials: improvement or cure of POP symptoms (feeling of something coming down, pressure, heaviness), using self-report or prolapse symptom questionnaire. Primary outcomes of prevention trials: prevention (non-development) of POP symptoms (feeling of something coming down, pressure, heaviness), using self-report or prolapse symptom questionnaire.

#### Secondary outcomes

##### 1) Women's observations

- Self reported prevention, improvement or cure of associated symptoms (urinary, bowel, sexual, abdominal or back pain).
- Satisfaction with outcome of treatment.
- Delay/avert need for alternative treatments such as PFMT, mechanical devices or surgery.
- Effectiveness of concurrent treatments such as PFMT, mechanical devices or surgery.

##### 2) Clinician's observations

- Objective prevention, improvement or cure of POP (e.g. using POP-Q system (Bump 1996).
- Pad test.
- Bowel function (e.g. evacuating proctography).

##### 3) Quality of life measures

- Prolapse-specific quality of life questionnaires.
- Generic quality of life or health status measures e.g. SF-36 (Ware 1992).
- Psychological/emotional well being outcome measures e.g. Hospital Anxiety and Depression Score (Zigmond 1983).
- Ability to cope with daily activities (work, social, leisure, domestic responsibilities etc.).



#### 4) Socio-economic measures

Cost-effectiveness measures (e.g. surgical operating time, number of pessaries used).

#### 5) Adverse effects

Vaginal irritation, vaginal discharge, infection or ulceration, urinary tract infection (cystitis), pain, intolerance/lack of compliance with oestrogen preparations, medical complications, effect on other existing medical conditions, other adverse effects such as endometrial hyperplasia, stroke and heart disease (particularly with long term treatment).

#### 6) Surgical outcomes

Recurrence of prolapse or development of *de novo* prolapse in another compartment.

Blood loss, surgical trauma such as damage to surrounding tissues or organs, operating time, infection, urinary tract infection / cystitis, haematoma.

#### 7) Outcomes that were not pre-specified

Outcomes that may be judged important when performing the review, but were not specified in the protocol.

Surrogate outcomes such as changes in serum hormone measurements or vaginal or urethral cytology maturation scores were reported in trials as evidence of compliance and of some oestrogenic effects, but their clinical significance is unclear. Flow and voiding cystometry or urodynamics were not considered as they are surrogate outcomes for urinary incontinence, and are not consistently related to other urinary outcomes.

### Search methods for identification of studies

We did not impose any language limitations on any of the searches detailed below.

#### Electronic searches

This review followed the Incontinence Group search strategy. Relevant studies were identified from the Incontinence Group Specialised Register of trials, which is included in *The Cochrane Library* (For more details of the search methods used to build the Specialised Register please see the 'Specialized Register' section of the Group's module in *The Cochrane Library*). The Register contains trials from MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL) and handsearching of journals and conference proceedings, including the International Continence Society meetings. Date of the most recent search of the Specialised Register for this review: 6 May 2010.

The trials in the Incontinence Group Specialised Register are also contained in CENTRAL.

The terms used to search the Incontinence Group Specialised Register are given below:

```
{(DESIGN.CCT*) OR {DESIGN.RCT*}) AND {TOPIC.PROLAPSE*} AND {INTVENT.CHEM.HORM*}
```

(All searches were of the keyword field of Reference Manager 9.5 N, ISI ResearchSoft).

For this review additional searches were performed by one of the review authors. These are detailed below.

MEDLINE was also searched separately, as a commonly used literature search database. Search terms included: pelvic organ prolapse, oestrogen, pelvic floor muscle training, pessary, vaginal repair, vaginal hysterectomy, sacrospinous fixation, pre spinous fixation, sacrocolpopexy, uterosacral suspension, colpoceleisis, mesh and posterior intravaginal slingplasty. The date of the last search covered January 1950 to April 2010 and was conducted in April 2010.

#### Searching other resources

We searched the reference lists of relevant articles.

### Data collection and analysis

Consumers were not involved in the design of the method or review process but commented on the completed review.

#### Selection of studies

All trials considered for the review were independently assessed by two review authors. Full papers were obtained for trials considered eligible, and also for those whose eligibility was unclear, to establish whether or not they met the inclusion criteria. Disagreements were resolved by discussion, and if necessary, by a third reviewer. Trials were excluded if they were not randomised or quasi-randomised.

#### Data extraction and management

Data extraction from individual trials was carried out by two review authors and compared. Discrepancies were resolved by discussion, and if necessary, by involving a third reviewer. We did not contact individual authors for data that was collected but not reported, reported in an unsuitable form for analysis, or from unpublished trials.

#### Assessment of risk of bias in included studies

Risk of bias of included trials were evaluated by two review authors, without prior consideration of the results. The criteria recommended by the Cochrane Incontinence Review Group were



used. Special attention was paid to randomisation process, adequacy of concealment of group allocation, and blinding during treatment and at outcome assessment (investigators, participants, health care providers and outcome assessors), adherence to intention-to-treat analysis, description of withdrawals and drop outs. Any difference in opinion between the two review authors was resolved by discussion, resorting to the opinion of a third reviewer if necessary.

### Measures of treatment effect

Data from included trials was analysed as described in the Cochrane Reviewers' Handbook (Higgins 2006) using Review Manager Version 5 (RevMan 5).

Risk ratio (RR) for dichotomous data and mean differences (MD) for continuous data, with 95% confidence intervals (CI) were used where trial data was available. The odds ratio was used in one case (for further details are provided in the Data Synthesis )

### Unit of analysis issues

No cross-over nor trials with clustering data were included.

### Assessment of heterogeneity

No significant heterogeneity was suspected from visual inspection of the results, hence the chi-squared test for heterogeneity or the I-squared statistic (Higgins 2003), to establish whether it was present or not, were not required.

### Data synthesis

Trials were only combined if the interventions were similar enough with regard to clinical criteria. Studies of oestrogen were not combined with SERMS.

No meta-analysis was conducted as trial level data was only available for at most a single study. One paper (Goldstein 2001) reported the results of a meta-analysis using fixed effect Mantel-Haenszel method with odds ratio as the summary measure. Both an overall result and a subgroup analysis of age was reported. As individual trial data were not reported the meta-analysis results are provided as reported in the original report.

### Subgroup analysis and investigation of heterogeneity

Two groups of women with POP were considered:

- A) those with symptomatic or asymptomatic pelvic organ prolapse (for treatment trials), and
- B) those without evidence of pelvic organ prolapse or a mixed population of women (with and without prolapse) at baseline (for prevention trials).

Subgroup analysis were planned for age, alternative forms of oestrogen preparations and combinations of management modalities, if presented in the included trials. A subgroup analysis of age was available for one comparison and is provided as reported in the original report.

### Sensitivity analysis

Sensitivity analysis for study quality could not be performed due to number of included studies.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### Results of the search

Six studies were identified by the search. Of these, two were not randomised and were therefore excluded, as shown in the Table of excluded studies.

### Included studies

Four studies were included in this review (Felding 1992; Goldstein 2001; Valente 2000; Vardy 2003). The total number of participants randomised between the trials was 7132 (although the vast majority, 6926, were from one meta-analysis of combined data from three RCTs, Goldstein 2001). Further details of these trials are shown in the Included Studies Table. There were no useable data reported in one trial (Valente 2000). Only published data were included in this review.

### Design

Three of the four studies (Felding 1992; Valente 2000; Vardy 2003) were randomised controlled trials and the fourth one (Goldstein 2001, N=6926) reported a secondary analysis of the adverse effects of SERMs (incidence of prolapse surgery) identified by three other randomised trials, two of which (Delmas 1997, N=601, Ettinger 1999, N=7705) were randomised controlled trials and the third (Johnston 2000) was a combined analysis of the one of the two (Delmas 1997, N=601) as well as a further un-referenced randomised controlled trial of a similar design (N=544).

### Sample sizes

Sample sizes ranged from 48 (Felding 1992) to 6,926 in the meta analysis (Goldstein 2001).

### Setting

Three trials were carried out in teaching university hospitals (Felding 1992; Valente 2000; Vardy 2003). The first (Felding 1992) was in Denmark, the second (Vardy 2003) was in the United States of America and the third (Valente 2000) in Rome, Italy. The fourth study (Goldstein 2001) was a meta-analysis of data from a combination of trials; one carried out in eight European countries (Delmas 1997); one carried out in the United States of America and Canada (Ettinger 1999); as well as a trial (Johnston 2000) reported as part of a combined analysis with Delmas 1997. No primary reference was identified for this third trial.

### Participants

#### (A) Treatment of prolapse

One trial (Felding 1992) included women who were at least one year postmenopausal and did not use any form of hormone replacement therapy for three months, while waiting for vaginal surgery for pelvic organ prolapse. The trial with no useable data (Valente 2000) included women with pelvic organ prolapse and urinary incontinence.

#### (B) Treatment and/or prevention of prolapse

Another trial (Vardy 2003) included healthy women who were at least six months postmenopausal and enrolled in an RCT for prevention of osteoporosis. This trial also examined the effects of oestrogens for the prevention of prolapse symptoms or on prolapse progression. Some of the women were being treated with a pessary for prolapse.

The final study (Goldstein 2001) was a secondary analysis of data from three randomised controlled trials in which women were at least two years postmenopausal and did not use any form of hormone replacement therapy for six months. The women had normal bone mineral density in one trial (Delmas 1997) and osteoporosis in another (Ettinger 1999). Women who had had a hysterectomy were excluded from the secondary analysis, to avoid the possible effect of hysterectomy on the pelvic floor. The remaining women included some with pelvic organ prolapse at the time of recruitment in the original trials as well as those without. It is not clear from the secondary analysis of these three trials (Goldstein 2001) if women were specifically asked about symptoms related to pelvic organ prolapse or examined for evidence of its presence in the original trials. The secondary analysis (Goldstein 2001) provided the combined incidence of urinary incontinence and pelvic

organ prolapse at recruitment. Therefore, it included women with pelvic organ prolapse at recruitment as well as those without. It is unclear whether measures were taken to prevent double counting of women from the various trials.

### Interventions

One trial (Felding 1992) randomised women to either 25 microgram oestradiol in a hydrophilic cellulose derived matrix tablet (Vagifem) or placebo vaginal tablet for three weeks before vaginal surgery for pelvic organ prolapse.

Another trial (Valente 2000) compared oral HRT (oestradiol plus progestogen) with calcium and Vitamin D.

A third one (Vardy 2003) randomised women into four groups receiving daily oral 0.625 mg of conjugated equine oestrogen, 20 mg of tamoxifen, 60 mg of raloxifene or placebo.

The fourth study (Goldstein 2001) was a secondary analysis of other trials of SERMs: one randomised women to either daily oral raloxifene 30, 60 or 150 mg or matching placebo for two years (Delmas 1997; Johnston 2000); and another trial randomised women to either daily oral raloxifene 60 or 120 mg plus supplemental calcium and cholecalciferol or matching placebo and supplemental calcium and cholecalciferol for three years (Ettinger 1999). However, the data have been merged irrespective of the different doses used as only summary outcomes were presented.

### Outcome measures

The trials included a variety of clinical and laboratory outcome measures.

One trial (Felding 1992) reported surgical, clinical and laboratory outcome measures up to four weeks after vaginal surgery for pelvic organ prolapse. All of these outcome measures fall within the group identified as secondary outcome measures for the purpose of this review. At three years, self-reported symptoms, frequency of urinary tract infection three years after the operation and the incidence of urinary tract infection in the postoperative period were reported in a separate article (Mikkelsen 1995).

The only relevant outcome measure in one study (Goldstein 2001) was surgery for pelvic organ prolapse, separately for women above and below 60 years of age, identified from a Clinical Trials Safety Database.

The outcome measures in the last trial (Vardy 2003) included hormonal assays; vitality of the vaginal and urethral mucosa by estimating the maturation value of the epithelial cells from a vaginal smear; and extent of pelvic organ prolapse, as judged by self-reported symptoms, modified POP-Q and Q-tip test, at baseline and after 20 weeks of treatment.

The outcome measures are reported in the [Included studies](#) table.

### Follow up

In one trial, [Felding 1992](#) reported outcomes at the time of performing vaginal surgery for pelvic organ prolapse, following three weeks of oestrogen/placebo treatment, at four weeks after surgery and at three years after surgery. The secondary analysis ([Goldstein 2001](#)) reported a cumulative incidence of surgery for pelvic organ prolapse at three years follow up. The other trial ([Vardy 2003](#)) reported outcomes following 20 weeks of treatment.

### Excluded studies

Two studies were excluded as they were not randomised ([Excluded studies](#)).

### Risk of bias in included studies

One trial did not provide enough data to assess risk of bias ([Valente 2000](#)).

### Allocation

In three included studies ([Felding 1992](#); [Goldstein 2001](#); [Vardy 2003](#)), random allocation relied on adequate sequence generation. Randomisation was described as double blind in one trial ([Felding 1992](#)), although no detail was provided. The trials included in the secondary analysis ([Goldstein 2001](#)) were described as randomised double blind controlled trials but no detail was given, other than indicating that block randomisation was used in one ([Delmas 1997](#)). More detail was provided in another trial ([Vardy 2003](#)) describing that random numbers were generated adequately.

### Blinding

In the trials included in three studies ([Felding 1992](#); [Goldstein 2001](#); [Vardy 2003](#)), both the treatment and placebo were described as 'matching' so that participants as well as the professionals who assessed the trial outcomes were blinded to treatment allocation. However, only one trial ([Vardy 2003](#)) confirmed that all active medications as well as placebo were identical in appearance and were provided in a non-gelatin containing capsule. All three reports indicated that the outcome assessors were blinded to the patient treatment protocol ([Felding 1992](#); [Goldstein 2001](#); [Vardy 2003](#)).

### Incomplete outcome data

One trial ([Felding 1992](#)) included 48 women, 24 in each of its two groups. There were two drop outs in the treatment group and one in the control group. Serum oestradiol levels were not measured in all women. At three year follow up after surgery, there were three drop outs in the treatment group and five in the control group from the original cohort. Another trial ([Goldstein 2001](#)) included data for all women included in the secondary analysis, which was

limited to women with intact uterus, bearing in mind that there were drop outs in the original trials [149 out of 601 ([Delmas 1997](#)), 877 out of 7705 ([Ettinger 1999](#))]. There were no drop outs in the other trial ([Vardy 2003](#)). However, pelvic organ prolapse quantification (POP-Q) was not carried out on all participants.

### Selective reporting

In two trials ([Goldstein 2001](#); [Vardy 2003](#)) data from women with pelvic organ prolapse at baseline were not reported separately from those without it, which made it difficult to extrapolate results and make conclusions for each of these two groups separately, as was planned in the review.

### Other potential sources of bias

One trial ([Goldstein 2001](#)) was a secondary analysis of data from three trials. The original trials were not focused on pelvic organ prolapse as an outcome, but rather bone density, fracture risk, serum lipid concentration and effect on the endometrium. The secondary analysis ([Goldstein 2001](#)) therefore did not look at pelvic organ prolapse per se, but rather the number of women who had prolapse surgery, reported as an adverse effect. In the fourth trial ([Vardy 2003](#)), significant, though small, differences in age and body mass index were noted between groups at baseline.

### Effects of interventions

The review was divided into two groups of women:

- (A) Treatment: those which treated women with symptomatic or asymptomatic prolapse, and
- (B) Prevention: those which prevented it or included a mixed population of women with and without prolapse (without reporting the data separately).

#### A. Treatment: postmenopausal women with symptomatic or asymptomatic pelvic organ prolapse.

Two trials included women, all of whom were thought to have prolapse ([Felding 1992](#); [Valente 2000](#)). No useable data were reported in one of these ([Valente 2000](#)).

##### 1. Oestrogen treatment alone versus no treatment/placebo

No trial compared oestrogen treatment alone versus no treatment.

##### 2. Oestrogen treatment alone versus another treatment

No trial compared oestrogen treatment alone versus another treatment.

### **3. Oestrogen treatment in conjunction with physical treatment (e.g. pelvic floor muscle training) versus physical treatment alone**

No trial compared oestrogen treatment in conjunction with physical treatment versus physical treatment as such.

### **4. Oestrogen treatment in conjunction with the use of vaginal pessaries versus the use of vaginal pessaries alone**

No trial compared oestrogen treatment in conjunction with the use of vaginal pessaries versus the use of vaginal pessaries alone.

### **5. Oestrogen treatment in conjunction with surgery versus surgery alone**

One trial (Felding 1992) randomised 48 women awaiting surgery for pelvic organ prolapse to either local oestrogen in the form of a vaginal tablet or a matching placebo for three weeks before operation. All women also had pelvic floor muscle training (PFMT) but the data are presented in this section because the aim of the oestrogen treatment was as an adjunct to surgery, not PFMT. Three women (two from the oestrogen + PFMT group and one from the placebo + PFMT group) dropped out before having surgery.

Long term outcomes included satisfaction (Analysis 5.1); recurrent prolapse (Analysis 5.2); urinary tract infections (Analysis 5.5); and urinary incontinence (Analysis 5.6). There were not enough data to reliably detect differences in these or any other short term outcomes, although fewer women had cystitis in the first four weeks after surgery (RR 0.21, 95% CI 0.05 to 0.85, Analysis 5.3). It is debatable whether this is of real clinical importance, as the trial was too small to reliably detect differences in any of the outcomes measured.

## **B. Prevention: postmenopausal women with or without pelvic organ prolapse but using oestrogen for another reason**

One trial (Vardy 2003) and one meta-analysis of three other trials (Goldstein 2001) included postmenopausal women. Both trials included some women with pelvic organ prolapse at the time of randomisation but outcome data were not grouped according to the presence or absence of pelvic organ prolapse.

### **1. Oestrogen or SERM treatment alone versus no treatment/placebo**

One paper provided a meta-analysis (Goldstein 2001) of data for women with intact uterus on recruitment from trials in which postmenopausal women were randomised to a range of doses of raloxifene (a SERM), with (Ertinger 1999) or without (Delmas 1997) calcium and calciferol supplements or matching placebo, to assess the effect of raloxifene on bone mineral density, risk of

fracture, serum lipid concentration and impact on endometrium. Participants with pelvic organ prolapse were not excluded and the results were not given according to whether women had pelvic organ prolapse on recruitment or not.

A significant reduction in the need for surgery at three years follow up was noted on raloxifene (35/4680 (0.75%) versus placebo, 34/2246 (1.51%), OR 0.50, 95% CI 0.31 to 0.81, Analysis 1.1), but this was significant only in women 60 years and older (OR 0.47, 95% CI 0.28 to 0.80, Analysis 1.1) and not in those younger than this age (OR 0.68, 95% CI 0.22 to 2.08, Analysis 1.1), when the results for these two age groups were looked at separately. However, the total number of women having prolapse surgery was small (69/6926), especially amongst women under the age of 60 years, and the confidence intervals in this group were wide.

### **2. Oestrogen treatment alone versus another treatment**

No trial compared oestrogen treatment alone versus another treatment, in women without pelvic organ prolapse.

### **3. Oestrogen or SERM treatment in conjunction with physical treatment (e.g. pelvic floor muscle training) versus physical treatment alone**

In one small trial, (Vardy 2003) postmenopausal women were randomised to either conjugated equine oestrogen, one of two selective oestrogen receptor modulators (tamoxifen or raloxifene) or placebo and all participants were asked to perform four sets of ten pelvic floor muscle contractions (Kegel's exercises) every day for 20 weeks. However, those using vaginal devices (pessaries) for pelvic organ prolapse were not excluded, no information was provided about the number of participants with pelvic organ prolapse and outcome data were not grouped according to whether participants had pelvic organ prolapse on recruitment or not. In addition, significant, though small, differences in age and body mass index were noted between groups at baseline. The results were presented separately for each drug.

It was not clear whether the SERMs (raloxifene and tamoxifen) had oestrogenic or anti-oestrogenic effects. A significant increase in serum sex hormone binding globulin (SHBG) level was noted on using conjugated equine oestrogen as well as the two selective oestrogen receptor modulators (tamoxifen and raloxifene) as compared to placebo. Significant increases in vaginal and urethral maturation index were noted only with using conjugated equine oestrogen, and not with the SERMs (tamoxifen and raloxifene) or placebo. No significant change in serum oestradiol or oestrone levels was noted in any group. However, the clinical significance of these findings is unclear.

The numbers were too small to detect significant differences between the groups in terms of the primary outcome, prolapse symptoms (Analysis 3.1), or urinary symptoms (Analysis 3.2) or change in objective prolapse measurements (Analysis 3.3).

#### **4. Oestrogen treatment in conjunction with the use of vaginal pessaries versus the use of vaginal pessaries alone**

No trial compared oestrogen treatment in conjunction with the use of vaginal pessaries versus the use of vaginal pessaries alone, in women without pelvic organ prolapse.

#### **5. Oestrogen treatment in conjunction with surgery versus surgery alone.**

No trial compared oestrogen treatment in conjunction with surgery versus surgery alone, in women without pelvic organ prolapse.

## **DISCUSSION**

### **Summary of main results**

#### **Treatment of prolapse**

Results from a single small trial (Felding 1992) where women were followed up to three years after prolapse surgery showed limited benefit from oestrogen treatment. No primary outcomes relating to prolapse symptoms were reported. The trial was too small to detect statistically significant improvement in the vaginal maturation index or epithelium thickness, levator ani muscle function, vaginal wall atrophy as noted by the surgeon at the time of surgery or the incidence of endometrial hyperplasia by using local oestrogen treatment for three weeks before surgery, in women who were also performing pelvic floor muscle training. No information was available regarding operative complications, including tearing of the vagina during surgery, estimated blood loss or need for blood transfusion. It could be argued that three weeks before surgery was too short a duration of treatment with oestrogen to allow physical or structural changes in pelvic structures to occur. Although three women (two of them treated with oestrogen) subsequently declined surgery, this may have been related to the effect of also performing PFMT.

Although there was no significant difference in the incidence of cystitis immediately after surgery, the incidence was significantly less in the subsequent four weeks in women who used local oestrogen as compared to the control group (RR 0.21, 95% CI 0.05 to 0.85, Analysis 5.3), though there was no significant difference in the incidence of recurrent cystitis thereafter, up to three years. This result was unexpected and needs to be confirmed in other trials. In addition, no significant difference was noted in satisfaction with the outcome of surgery or the development of urinary incontinence three years later.

#### **Prevention of prolapse**

For the prevention of pelvic organ prolapse, results from a single trial (Vardy 2003), and a secondary analysis of three other trials (Goldstein 2001, primarily aimed at treating osteoporosis with SERMs and including women with and without pelvic organ prolapse), showed some benefit. A significant reduction in the need for surgery for pelvic organ prolapse was found in the women treated with raloxifene and tamoxifen, but this was shown to be limited to women older than 60 years when the data were analysed by age (Analysis 1.1). Another trial (Vardy 2003) was too small to detect change in pelvic organ prolapse stage or prolapse or urinary symptoms with oestrogen, raloxifene or tamoxifen.

#### **Summary**

It appears, therefore, that local oestrogen may have a weak beneficial effect in reducing the incidence of urinary tract infection after prolapse surgery. It also appears that the oral SERM raloxifene may have a beneficial effect in reducing the need for prolapse surgery in women who are older than 60 years, but whether this is because of an oestrogenic or another effect is unclear and cannot be taken as a recommendation for practice. There is need for further research to confirm these findings and elucidate them further in terms of effect on prolapse symptoms, quality of life and cost effectiveness.

#### **Overall completeness and applicability of evidence**

It is important to look at the findings of this review within the context of its aim. The review was intended to explore the value of oestrogens in preventing as well as managing pelvic organ prolapse using various systemic and local forms of treatment in terms of self-reported and objective outcomes, including quality of life, cost effectiveness and adverse events. Whilst some of these aspects were covered in the studies found and included in the review, such as symptoms of prolapse and need for surgery, others, such as quality of life and cost effectiveness, were not explored in any of the trials found and were not therefore addressed in this review. The lack of quality of life and other self-reported outcome measures, such as satisfaction with using oestrogen for prevention or treatment of pelvic organ prolapse further underlines the lack of evidence in relation to perception of the treatment and how it affects women's day to day activities.

There is not enough attention paid to the social impact of pelvic organ prolapse and the possible health promotion value of using oestrogen in its prevention and management. This extends to certain occupations and patient groups at more risk of pelvic organ prolapse, for example as a result of heavy lifting. Women with pre-existing medical problems such as obesity or medical conditions that preclude anaesthesia may benefit from oestrogen treatment alone or concomitantly with pessaries. Women who have a contra-



indication to the use of systemic oestrogen, for example after treatment of breast cancer, may still be able to use local preparations. None of the trials made specific reference to anterior, upper or posterior compartments and all trials grouped pelvic organ prolapse as a single category. This adds to the paucity of evidence in assessing the value of oestrogen for pelvic organ prolapse, which in turn calls for more research into this area.

In summary, the lack of evidence means that health care staff do not have enough information to offer women regarding the use of oestrogen as prevention or treatment for pelvic organ prolapse symptoms, as there is no information about benefit and risk, route of application or duration of use. Despite this total lack of evidence, oestrogens are commonly used in clinical practice to treat postmenopausal women with prolapse symptoms, before and/or after prolapse surgery, and in conjunction with pessaries or PFMT.

### Quality of the evidence

Randomised controlled trials provide the highest level of evidence as they eliminate selection bias. Although all trials included in this review reported randomised controlled trials, they had other methodological features that limited their value in assessing whether oestrogen, alone or in conjunction with other forms of treatment for pelvic organ prolapse, is effective in treating and/or preventing pelvic organ prolapse. None of the trials was based on a power calculation. Only four studies were identified: two involving participants with pelvic organ prolapse and two involving participants with as well as without pelvic organ prolapse.

Although one of the trials, (Goldstein 2001) included 6926 participants, it was not actually planned to assess the impact of oestrogen on pelvic organ prolapse, but rather it was a secondary analysis of trials that assessed the effect of raloxifene on bone mineral density, risk of fracture, serum lipid concentration and the endometrium. The other trials (Felding 1992; Vardy 2003) included a relatively small number per group, 24 in one trial (Felding 1992) and 13 to 15 in another (Vardy 2003). Two of the trials (Goldstein 2001; Vardy 2003) included a mixture of participants with as well as without pelvic organ prolapse, without separating the two groups. In one trial (Felding 1992), serum oestradiol levels were not measured in all participants. In another, (Vardy 2003), significant, though small, differences in age and body mass index were noted between groups at base line and pelvic organ prolapse quantification (POP-Q) was not carried out on all participants.

The review was developed and carried out by professionals without consumer involvement although consumers refereed the final review. All of these factors need to be taken into consideration when looking at the findings of this review.

## AUTHORS' CONCLUSIONS

### Implications for practice

There was limited evidence that local oestrogen in conjunction with pelvic floor muscle training for three weeks before surgery may reduce the incidence of post-operative cystitis (UTI). There was also evidence that oral raloxifene (SERM) may reduce the need for surgery for pelvic organ prolapse in women over the age of 60 years but this cannot be taken as a recommendation for practice. This evidence is based on single trials and does not explore the full potential for oestrogens in relation to prevention as well as treatment of pelvic organ prolapse.

### Implications for research

There is a need for well organised randomised controlled trials with adequate sample size, validated outcome measures and long term follow up to assess the value of various forms of oestrogen preparations in the prevention as well as management of pelvic organ prolapse. These trials need to address various compartments and include objective as well as self-reported outcome measures, quality of life assessment and cost effectiveness. Different routes of administration and potential adverse effects also need to be evaluated.

Two main research questions urgently need to be addressed by such RCTs. Postmenopausal women whose prolapse is being managed using a pessary or device are commonly treated with local oestrogens, either prophylactically or if complications (such as erosion, bleeding or discharge) occur. The effectiveness and cost effectiveness of these strategies need to be defined in terms of self-reported symptoms, adverse effects and costs. Secondly, women who are having prolapse surgery are often treated with oestrogens before and/or after operation. An RCT in this group should measure self-reported prolapse symptoms after surgery as the primary outcome but should also record surgical complications, adverse events, recurrence of prolapse and quality of life.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Felding 1992

Methods	Randomised controlled double blind trial Setting: University Hospitals, Denmark
Participants	48 women (24 in the treatment group and 24 in the control group) Drop outs: A: 2, B: 1 (as the oestrogen and pelvic floor muscle training made the operation unnecessary) Availability at 3 year follow up (Mikkelsen 1995): A: 21, B: 19 Inclusion: women undergoing surgery for pelvic organ prolapse, >1 year after the menopause. Exclusion: Hormone replacement therapy within the previous 3 months, breast, uterine or other hormone-dependent cancer, genital bleeding of unknown origin, thrombophlebitis, cardiac insufficiency treated with digitalis, steroid treatment. Prolapse surgery included vaginal hysterectomy, anterior and/or posterior vaginal wall repair, Manchester/Fothergill operation or combination.
Interventions	A (22): daily 25 mcg oestradiol in a hydrophilic cellulose derived matrix (Vagifem) vaginal tablets B (23): matching daily placebo vaginal tablets All had pelvic floor muscle training pre-operatively (success evaluated before and 4 weeks after operation) Duration of treatment: 3 weeks before surgery Follow up: 4 weeks and 3 years after surgery. None of the women received hormone replacement therapy after the operation.
Outcomes	Vaginal smears were obtained before trial, at surgery and 4 weeks after surgery and used to calculate the maturation (oestrogen) index Oestrogen index at surgery: A: mean 54.97 (SD 4.78), B: 53 (6.14) (P<0.001) Oestrogen index 4 weeks after surgery: A: 51.96 (SD 1.22), B: 51.02 (3.69), not significant A highly significant difference (P<0.001) was observed in the treatment group at surgery but not at 4 weeks follow up Tablets were well tolerated in both groups Vaginal wall epithelium thickness was estimated from vaginal biopsies obtained before treatment and during surgery: A: 0.271 mm (SD 0.108), B: 0.233 (0.144) (P=0.017) The surgeons assessed vaginal wall for atrophy at the time of operation and judged whether women were treated with local hormone replacement therapy or not Vaginal wall judged atrophic during operation: A: 5/22, B: 4/23 Suspicion of being on local hormone replacement therapy: A: 13/22, B: 13/23 Levator ani function was assessed clinically by vaginal examination before and 4 weeks after surgery, no further detail was provided however, levator ani function improved: A: 6/22, B: 6/23 Cystitis immediately after surgery: A: 3/22, B: 8/23 Cystitis within 4 weeks following surgery: A: 2/22, B: 10/23 (P=0.02) Recurrent cystitis: A: 2/22, B: 8/23 Endometrial curettage at the time of surgery, endometrial hyperplasia: A: 2/22, B: 0/23 (simple endometrial hyperplasia without epithelial atypia which disappeared in 1 month). One woman menstruated, but no information was given as to whether she belonged to the treatment group or the placebo group.

**Felding 1992** (Continued)

	<p>Systemic hormonal impact was assessed at baseline, after 3 weeks of therapy and 4 weeks after surgery.  Serum oestradiol level was measured in 12 women in each group.  Serum follicle stimulating hormone was measured in 16 women in each group.  No difference was noted between the two groups.  <b>At 3 years after the operation:</b>  Later recurrent UTIs: A: 4/21, B: 2/19  Women satisfied with surgical outcome: A: 14/21, B 14/19  Recurrence of pelvic organ prolapse: A: 5/21; B 5/19  Repeat surgery for pelvic organ prolapse: 2, but unclear in which group.  Stress incontinence of urine: A: 3/21; B: 4/19</p>	
Notes	<p>No comment on funding  No data was provided about sufficient cleavage, estimated blood loss or complications of tablet use  Groups were comparable at baseline on age, age at menopause, weight, height, blood pressure and vaginal wall thickness  Outcomes assessed by pathologist blinded to treatment allocation  One woman died before the 3 year follow up, but it was unclear from which group</p>	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Unclear	Randomised controlled double blind trial
Blinding? All outcomes	Yes	Women, surgeons and histopathologists blinded to treatment allocation. No statement made regarding what the active pessary and placebo looked like.

**Goldstein 2001**

Methods	<p>Secondary analysis of 3 published RCTs. Two of these were randomised controlled double blind trials (N=601, Delmas 1997; N=7705, Ettinger 1999) and the third provided a combined analysis of data from Delmas (N=601) and another identical randomised controlled trial (N=544) (Johnston 2000, combined N=1145).  Setting: 8 European countries in one randomised controlled trial (Delmas 1997) and the United States of America and Canada in another (Ettinger 1999). The third study (Johnston 2000) included data from the first one (Delmas 1997), which was carried out in 8 European countries, in addition to data from another randomised controlled study that was carried out in the United States of America and Canada.</p>
Participants	<p>6926 women with intact uterus at inclusion in the 3 trials, out of an original combined cohort of 8850 women  These included 969 out of 1145 healthy postmenopausal women (Delmas 1997; Johnston 2000) and 5957 out of 7705 postmenopausal women with osteoporosis (Ettinger 1999).  Drop outs: Although there were drop outs in the original studies [149/601 (Delmas 1997), 877/</p>

**Goldstein 2001** (Continued)

	<p>7705 (Ettinger 1999)], there were no missing data for the women included in the secondary analysis (Goldstein 2001).</p> <p>Inclusion: (1, 2) healthy postmenopausal women (Delmas 1997; Johnston 2000), (3) postmenopausal women with confirmed osteoporosis (Ettinger 1999).</p> <p>Exclusion: women taking oestrogen, progestins, androgens or systemic steroids within 6 months prior to participation and those with unexplained vaginal bleeding from 2 RCTs (Delmas 1997, Ettinger 1999).</p> <p>Women who had hysterectomy were excluded from the secondary analysis (Goldstein 2001).</p> <p>There was no significant difference at baseline in age, duration past the menopause, body mass index, lumbar spine bone mass density, incidence of vertebral fracture, ethnic origin, previous use of hormone replacement therapy, percentage of smokers and alcohol users, stress incontinence of urine or pelvic organ prolapse.</p>
Interventions	<p>A (4680): oral raloxifene 30, 60 or 150 mg per day for 2 years in one study (Delmas 1997), raloxifene 60 or 120 mg per day plus supplemental calcium and cholecalciferol for 3 years in another study (Ettinger 1999).</p> <p>B (2246): matching placebo in 2 studies (Delmas 1997 and Johnston 2000) and matching placebo with calcium and cholecalciferol in the third one (Ettinger 1999).</p> <p>The study by Johnston 2000 reported 3 year data. All women from the three studies (Delmas 1997; Ettinger 1999; Johnston 2000) were pooled together for the purpose of the secondary analysis (Goldstein 2001).</p> <p>All participants were followed up for 3 years.</p>
Outcomes	<p>The incidence of surgery for pelvic organ prolapse was recorded in the Clinical Trials Safety Databases.</p> <p>Surgery for pelvic organ prolapse: A: 35/4680 (0.75%) , B 34/2246 (1.51%), OR 0.50 (95% CI 0.31 to 0.81) (P 0.003). The trend was observed after 9 months of treatment and was sustained for 3 years of treatment.</p> <p>Subgroup analysis by age:</p> <p>Women younger than 60 years: A: 8 (0.55%), B 5 (0.85%), adjusted OR 0.68 (95% CI 0.22 to 2.08, P=0.494), not statistically significant.</p> <p>Women of 60 years or older: A: 27 (0.84%), B: 29 (1.75%), adjusted OR 0.47 (95% CI 0.28 to 0.80, P &lt; 0.005), statistically significant.</p>
Notes	<p>The trials included in the secondary analysis were not designed to look at pelvic organ prolapse. Consequently, the analysis only measured the incidence of surgery for prolapse. Similarly, some factors that can affect the incidence of pelvic organ prolapse, such as number and mode of delivery, were not recorded in the three trials, hence it was not possible to determine baseline comparability. In addition, the women received different doses of raloxifene. Finally, adverse events reported in the individual trials have not been abstracted separately.</p>

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Yes	All original trials included in the secondary analysis had random allocation.

**Goldstein 2001** (Continued)

Blinding? All outcomes	Yes	All original trials included in the secondary analysis blinded both women and the health care staff looking after them. No statement about what the medication and placebo looked like.
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**Valente 2000**

Methods	RCT 'randomly allocated to 2 groups' Setting: Rome, Italy
Participants	100 women Inclusion: prolapse of the pelvic floor and urinary incontinence
Interventions	A (50): calcium 100 mg + Vitamin D 880 IU B (50): oral HRT (oestradiol 0.625 mg + MAP 5 mg) Duration of treatment: 12 months Follow up: unclear
Outcomes	Subcutaneous collagen thickness increased in both groups Symptoms decreased in both groups Data unclear but authors concluded that both treatments result in 'collagen thickness reactivation'
Notes	Abstract only No data on baseline comparability of groups No useable data

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information
Allocation concealment?	Unclear	No information
Blinding? All outcomes	Unclear	No information

**Vardy 2003**

Methods	Randomised controlled double blind trial for prevention of osteoporosis. Setting: 2 University Hospitals, in New York, in the United States of America.
Participants	58 postmenopausal women (15 in each of the three intervention groups and 13 in the control group). Dropouts: None Inclusion: At least 1 year after menopause, age 45 to 70 years, normal mammogram within 6



	<p>months, able to perform Kegel's exercises upon instruction.</p> <p>Exclusion: Non white women, serious acute or chronic medical disorder, previous hysterectomy or reconstructive pelvic surgery, oestrogen, calcitonin, fluoride, steroid or diuretic therapy within 6 months, contraindication to hormone replacement therapy or selective oestrogen receptor modulators (SERMs).</p> <p>Women using vaginal pessaries for pelvic organ prolapse were not excluded.</p>
Interventions	<p>A (15): daily oral 0.625 mg of conjugated equine oestrogen</p> <p>B (15): daily oral 60 mg of raloxifene</p> <p>(15): daily oral 20 mg of tamoxifen</p> <p>D (13): daily oral matching placebo</p> <p>All participants were asked to perform 4 sets of 10 Kegel exercises every day</p> <p>Duration of treatment: 20 weeks</p> <p>Follow up: at the end of treatment</p>
Outcomes	<p>POP-Q (at baseline and at the end of treatment). This was not performed in all participants:</p> <p>A: 2/8 improved POP-Q score, 2/8 worsened POP-Q score</p> <p>B: 8/12 worsened POP-Q score, 1/12 worsened POP-Q stage</p> <p>C: 4/13 worsened POP-Q score</p> <p>D: 2/11 worsened POP-Q score</p> <p>Any indicator of prolapse (self-categorisation of their symptoms at the end of treatment):</p> <p>A: 22% had increased indication (2/8)</p> <p>B: 75% had increased indication (8/12)</p> <p>C: 60% had increased indication (8/13)</p> <p>D: 18% had increased indication (2/11)</p> <p>One week diary of urinary symptoms (urgency, frequency and incontinence) as well as vaginal dryness, dyspareunia and discharge (at baseline, during each week of the study and at the end of treatment):</p> <p>A: 3/15 improved urinary symptoms, 2/15 worsened urinary symptoms</p> <p>B: 2/15 improved urinary symptoms, 1/15 worsened urinary symptoms</p> <p>C: 1/15 new onset pressure symptoms, 4/15 worsened urinary symptoms</p> <p>D: 3/13 worsened urinary symptoms</p> <p>Cotton swab test for women with stress incontinence (at baseline and at the end of treatment)</p> <p>A: 2/2</p> <p>B: 3/5 increased deflection</p> <p>C: 5/8 increased deflection</p> <p>D: 0/4</p> <p>Dyspareunia: A: 1/15, B: 0/15, C: 0/15, D: 1/13</p> <p>Serum oestradiol, oestrone and serum hormone binding globulin levels (at baseline and at the end of treatment)</p> <p>Significant increase in serum sex hormone binding globulin level in the three treatment groups (A, B, C) but not in the placebo group (D)</p> <p>No significant change in serum oestradiol or oestrone level in any group (A, B, C, D)</p> <p>Vaginal and urethral cytology to estimate the maturation value (at baseline and at the end of treatment)</p> <p>Significant increase in vaginal and urethral maturation value was noted with conjugated equine estrogen (group A)</p> <p>No significant change in vaginal or urethral maturation value with tamoxifen (group B), raloxifene (group C) or placebo (group D)</p>

**Vardy 2003** (Continued)

	A non-significant reduction was noted in vaginal, but not in urethral, maturation value with raloxifene (group C) Vaginal and urethral maturation values correlated with oestradiol and oestrone levels in all groups The difference between conjugated equine oestrogen and placebo on one hand and tamoxifen and raloxifene on the other was significant (P 0.015)	
Notes	Statistically significant, though small, differences in age and body mass index were noted between the groups at baseline.	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Computer generated numbers
Allocation concealment?	Unclear	No information ('randomised')
Blinding? All outcomes	Yes	All tablets were identical in appearance and provided in a non-gelatin containing capsule.

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

Study	Reason for exclusion
Barber 2002	Non randomised study
Verheul 2007	Non randomised study

## DATA AND ANALYSES

### Comparison 1. Oestrogen / SERM treatment alone versus no treatment/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of women requiring surgery for prolapse			Other data	No numeric data

### Comparison 3. Oestrogen / SERM treatment + PFMT versus PFMT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of women with worsening prolapse symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Oestrogen versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Raloxifene versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Tamoxifen versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Number of women with worsening urinary symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Oestrogen versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Raloxifene versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.3 Tamoxifen versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Number of women with worsening prolapse stage (POP-Q)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Oestrogen versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Raloxifene versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 Tamoxifen versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

### Comparison 5. Oestrogen / SERM treatment + surgery versus surgery alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of women satisfied with surgery 3 years later	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Oestrogen + PFMT + Surgery	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Recurrent prolapse 3 years later	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Oestrogen + PFMT + Surgery	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

3 Cystitis within 4 weeks following surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Development of cystitis immediately after surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Long-term recurrent UTIs	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Urinary incontinence 3 years later	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Endometrial hyperplasia	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Improved levator ani function before surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Vaginal epithelium thickness at surgery (mm)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Oestrogen + PFMT + Surgery	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
10 Number of women with vaginal wall atrophy at surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Oestrogen + PFMT + Surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Oestrogen Index at surgery	1	Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Oestrogen + PFMT + Surgery	1	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Oestrogen Index 4 weeks after surgery	1	Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Oestrogen + PFMT + Surgery	1	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable

**Analysis 1.1. Comparison 1 Oestrogen / SERM treatment alone versus no treatment/placebo, Outcome 1 Number of women requiring surgery for prolapse.**

**Number of women requiring surgery for prolapse**

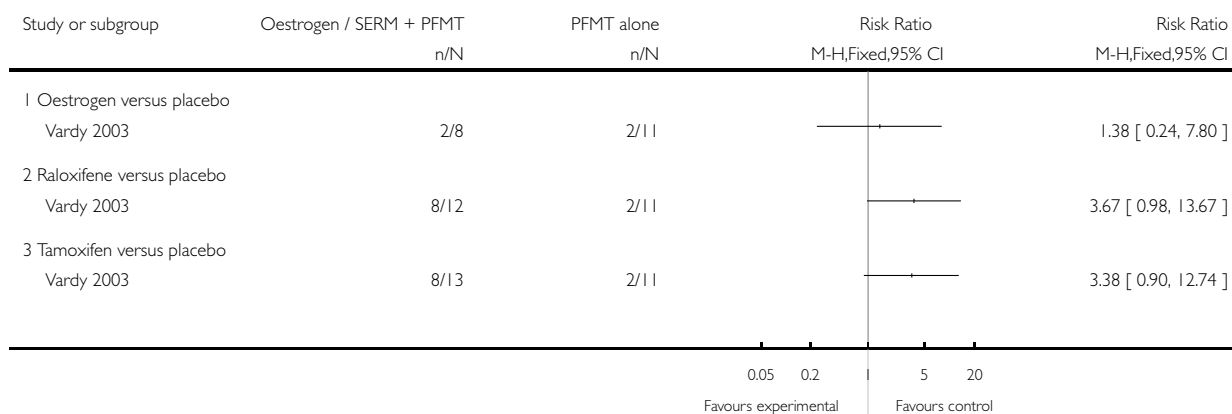
Study	Heading 1	Heading 2	Heading 3	Heading 4	Heading 5
Goldstein 2001	All women	OR=0.50	95% CI 0.31 to 0.81	Raloxifene (0.75%) 35/4680	Placebo 34/2246 (1.51%)
Goldstein 2001	Age < 60 years	OR=0.68	95% CI 0.22 to 2.08	8/1454	5/588
Goldstein 2001	Age >= 60 years	OR=0.47	95% CI 0.28 to 0.80	27/3226	29/1658

### Analysis 3.1. Comparison 3 Oestrogen / SERM treatment + PFMT versus PFMT alone, Outcome 1 Number of women with worsening prolapse symptoms.

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 3 Oestrogen / SERM treatment + PFMT versus PFMT alone

Outcome: 1 Number of women with worsening prolapse symptoms

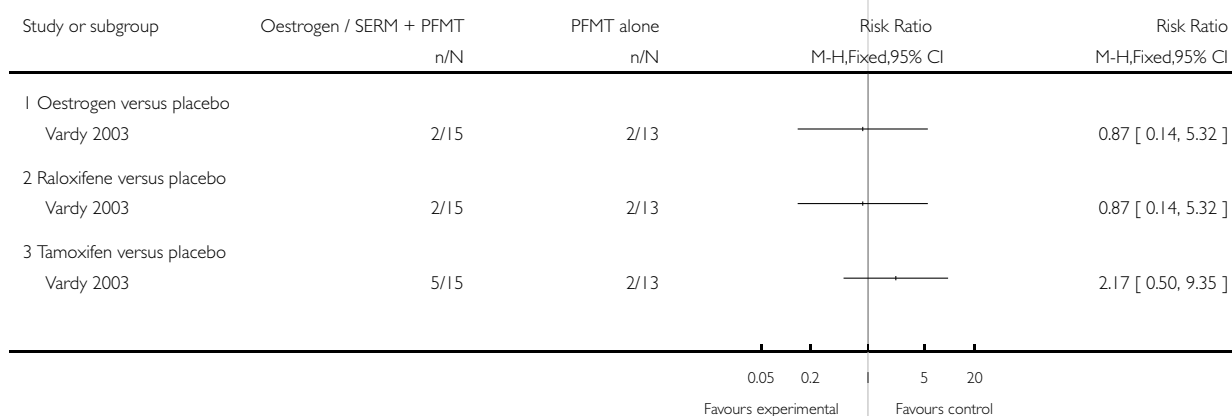


### Analysis 3.2. Comparison 3 Oestrogen / SERM treatment + PFMT versus PFMT alone, Outcome 2 Number of women with worsening urinary symptoms.

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 3 Oestrogen / SERM treatment + PFMT versus PFMT alone

Outcome: 2 Number of women with worsening urinary symptoms

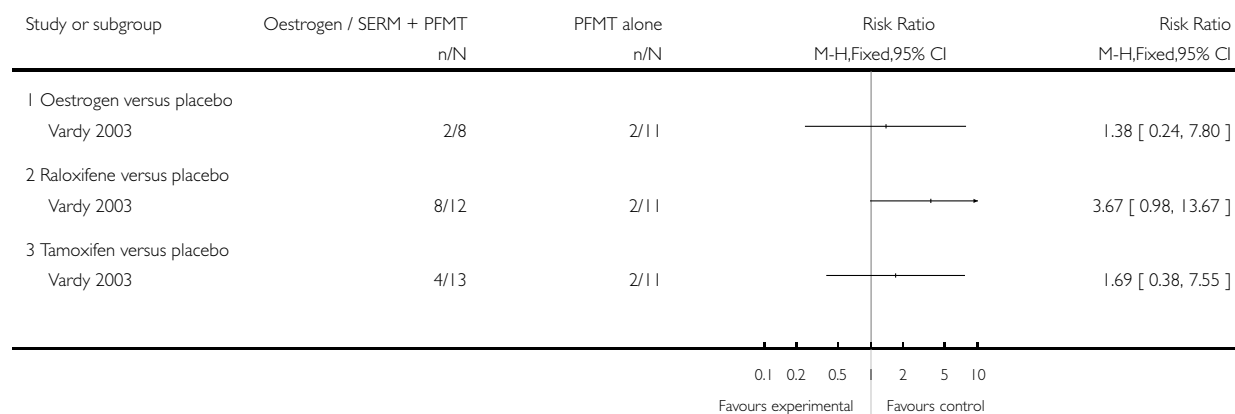


**Analysis 3.3. Comparison 3 Oestrogen / SERM treatment + PFMT versus PFMT alone, Outcome 3 Number of women with worsening prolapse stage (POP-Q).**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 3 Oestrogen / SERM treatment + PFMT versus PFMT alone

Outcome: 3 Number of women with worsening prolapse stage (POP-Q)

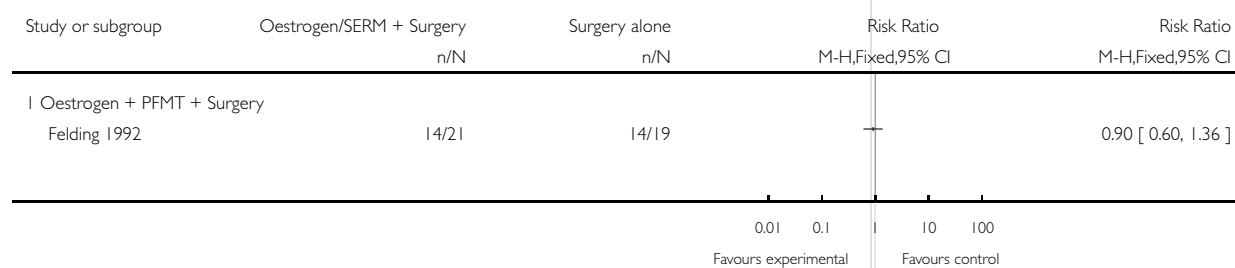


**Analysis 5.1. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 1 Number of women satisfied with surgery 3 years later.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 1 Number of women satisfied with surgery 3 years later

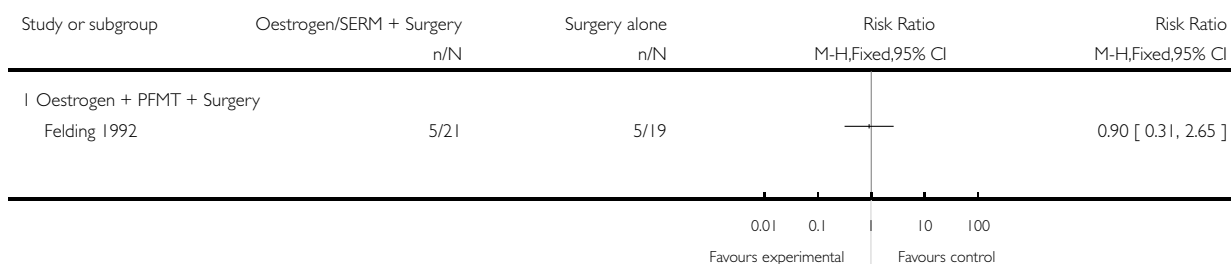


**Analysis 5.2. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 2 Recurrent prolapse 3 years later.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 2 Recurrent prolapse 3 years later

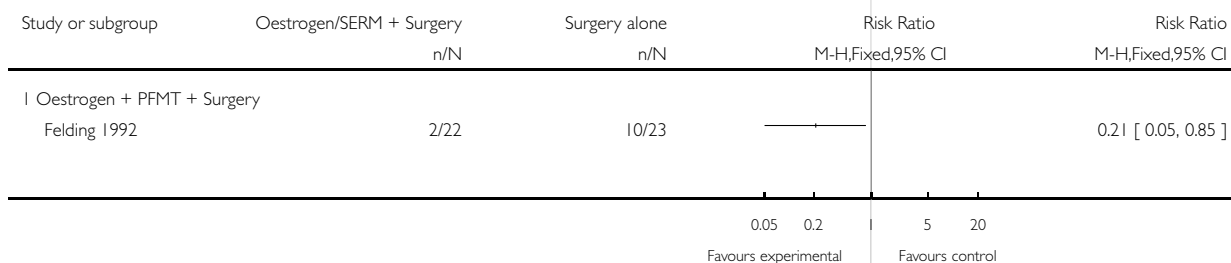


**Analysis 5.3. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 3 Cystitis within 4 weeks following surgery.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 3 Cystitis within 4 weeks following surgery





**Analysis 5.4. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 4 Development of cystitis immediately after surgery.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 4 Development of cystitis immediately after surgery

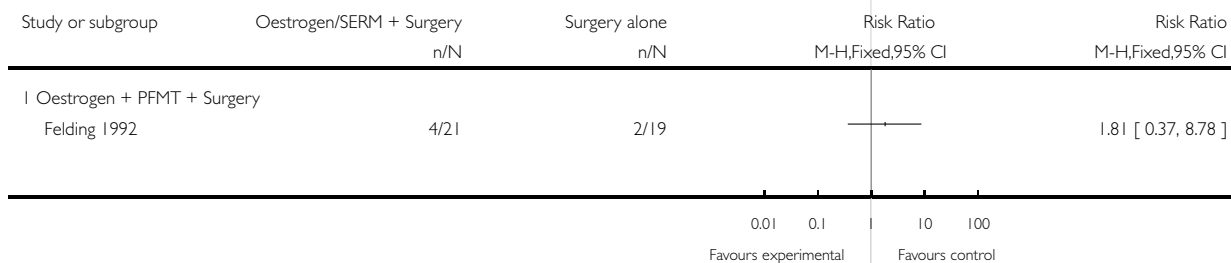


**Analysis 5.5. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 5 Long-term recurrent UTIs.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 5 Long-term recurrent UTIs

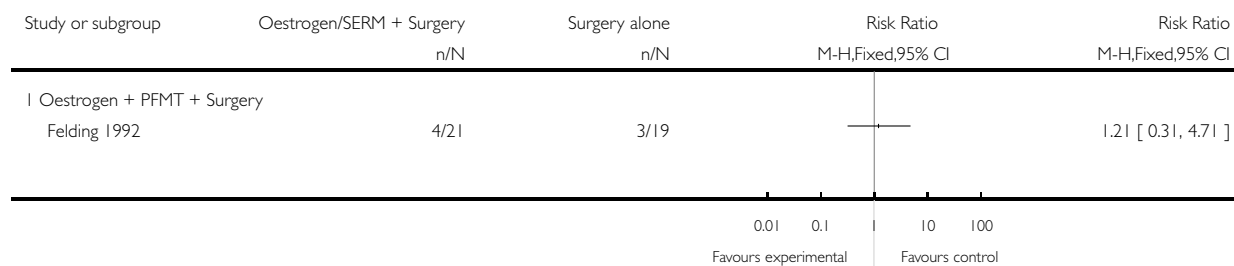


**Analysis 5.6. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 6 Urinary incontinence 3 years later.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 6 Urinary incontinence 3 years later

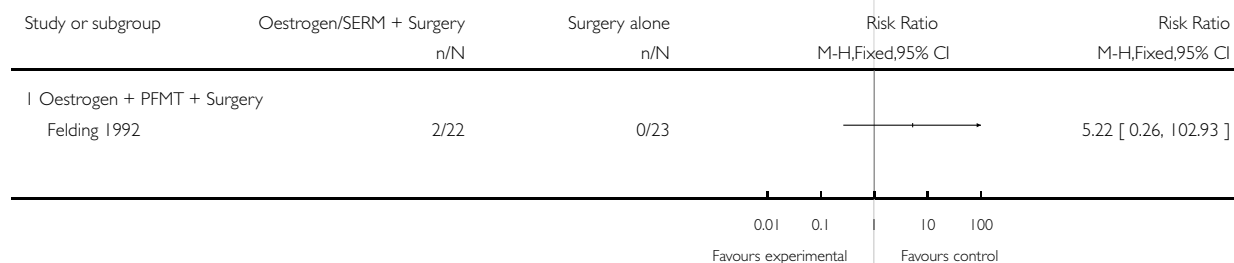


**Analysis 5.7. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 7 Endometrial hyperplasia.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 7 Endometrial hyperplasia



**Analysis 5.8. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 8 Improved levator ani function before surgery.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 8 Improved levator ani function before surgery

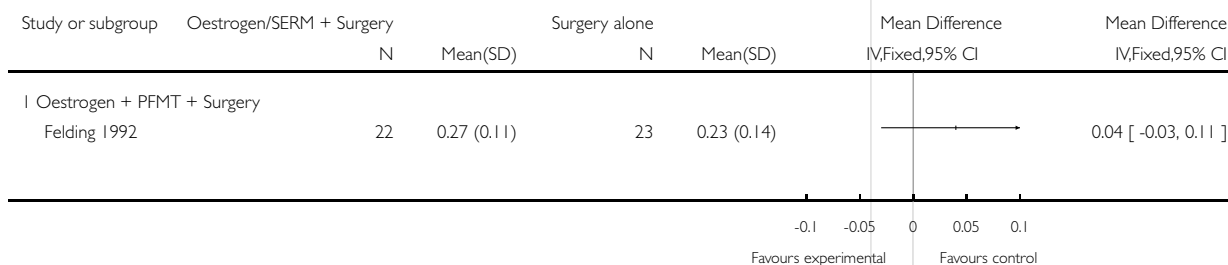


**Analysis 5.9. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 9 Vaginal epithelium thickness at surgery (mm).**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 9 Vaginal epithelium thickness at surgery (mm)

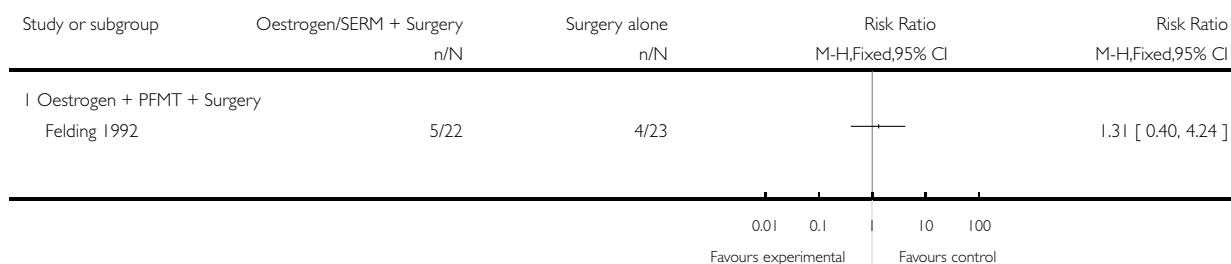


**Analysis 5.10. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 10  
Number of women with vaginal wall atrophy at surgery.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 10 Number of women with vaginal wall atrophy at surgery

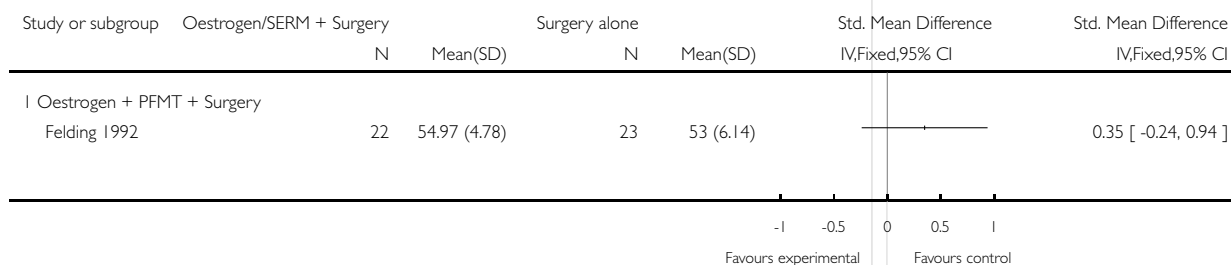


**Analysis 5.11. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 11  
Oestrogen Index at surgery.**

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 11 Oestrogen Index at surgery



### Analysis 5.12. Comparison 5 Oestrogen / SERM treatment + surgery versus surgery alone, Outcome 12 Oestrogen Index 4 weeks after surgery.

Review: Oestrogens for treatment or prevention of pelvic organ prolapse in postmenopausal women

Comparison: 5 Oestrogen / SERM treatment + surgery versus surgery alone

Outcome: 12 Oestrogen Index 4 weeks after surgery

Study or subgroup	Oestrogen/SERM + Surgery		Surgery alone		Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)		
I Oestrogen + PFMT + Surgery Felding 1992	22	51.96 (1.22)	23	51.02 (3.69)		0.33 [ -0.26, 0.92 ]

## HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 9, 2010

## CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of the review.

## DECLARATIONS OF INTEREST

None.

## SOURCES OF SUPPORT

### Internal sources

- None, Not specified.

### **External sources**

- No sources of support supplied

### **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

The title and review were amended to reflect the inclusion of trials of drugs which might have oestrogenic or anti-oestrogenic effects (SERMs) although they are not actually classed as oestrogens. The review was further divided into (A) treatment for prolapse and (B) prevention of prolapse symptoms or progression.