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Hormone replacement for osteoporosis in women with primary biliary cirrhosis

Jelena S Rudic1, 5, Goran Poropat2, Miodrag N Krsitic3, Goran Bjelakovic4, 5, Christian Gluud5

1Department of Hepatology, Clinic of Gastroenterology, Clinical Centre of Serbia, Belgrade, Serbia. 2Department of Gastroenterology, Clinical Hospital Centre Rijeka, Rijeka, Croatia. 3Clinic of Gastroenterology, Clinical Centre of Serbia, Belgrade, Serbia. 4Department of Internal Medicine, Medical Faculty, University of Nis, Nis, Serbia. 5The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 3344, Righospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Contact address: Jelena S Rudic, jelena_rudic@yahoo.com.

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ABSTRACT

Background

Women with primary biliary cirrhosis often suffer from postmenopausal osteoporosis due to their age, or osteoporosis secondary to their liver disease, or treatments provided for their liver disease. Hormone replacement increases bone mineral density and reduces fractures in postmenopausal women. On the other hand, hormone replacement increases the risk of various adverse events. We could not identify any meta-analyses or systematic reviews on hormone replacement in women with primary biliary cirrhosis.

Objectives

To assess the beneficial and harmful effects of hormone replacement for osteoporosis in women with primary biliary cirrhosis.

Search methods

The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, and full text searches were conducted until November 2011. Manufacturers and authors were contacted during the review conductance.

Selection criteria

All randomised clinical trials of hormone replacement in primary biliary cirrhosis administered by any route, or regimen, or dose compared with placebo or no intervention.

Data collection and analysis

Two authors extracted data. RevMan Analysis was used for statistical analysis of dichotomous data with risk ratio (RR) or risk difference (RD) and of continuous data with mean difference (MD), all with 95% confidence intervals (CI). Methodological domains were used to assess risk of systematic errors (bias). Trial sequential analysis was used to control for random errors (play of chance).
Main results

Two trials with 49 participants were included. One trial had low risk of bias. The other trial had high risk of bias. Hormone replacement had no effect on all-cause mortality (RD 0.00; 95% CI -0.11 to 0.11; $I^2 = 0\%$) and fractures (RD -0.08; 95% CI -0.24 to 0.07, $I^2 = 0\%$). Hormone replacement significantly increased adverse events and number of patients having hormone replacement withdrawn due to adverse events (RR 5.26; 95% CI 1.26 to 22.04, $I^2 = 0\%$). Hormone replacement had no significant effect on lumbar spine bone mineral density (MD 1.25 g/cm² year⁻¹; 95% CI -0.91 to 3.42, $I^2 = 0\%$). On the other hand, a significant increase in proximal femur bone mineral density was observed in the control group (MD 2.24 g/cm² year⁻¹; 95% CI 0.74 to 3.74, $I^2 = 0\%$). Hormone replacement had no significant effect on liver-related mortality, liver transplantation, or liver-related morbidity. Hormone replacement had no significant effect on serum bilirubin concentration (MD 4.60 µmol/L; 95% CI -3.42 to 12.62, $I^2 = 0\%$).

Authors’ conclusions

We did not find evidence to support the use of hormone replacement for women with primary biliary cirrhosis. It seems that hormone replacement is connected with a significant increase in the occurrence of adverse events.

**PLAIN LANGUAGE SUMMARY**

Hormone replacement for osteoporosis in women with primary biliary cirrhosis

Patients with primary biliary cirrhosis are mainly elderly women who are naturally prone to osteoporosis. Hormone replacement has been used worldwide to treat symptoms of menopause and to prevent chronic conditions such as osteoporosis. However, hormone replacement is associated with an increase in adverse events, several of which are serious. This review assessed the effect of hormone replacement on treatment of osteoporosis in women with primary biliary cirrhosis. We found no evidence of effect of hormone replacement on mortality and fractures in women with primary biliary cirrhosis. It seems that hormone replacement given to women with primary biliary cirrhosis is connected with a significant increase in the occurrence of adverse events compared with placebo or no intervention. Hormone replacement appears to have no effect on the lumbar bone mineral density compared with placebo or no intervention. Hormone replacement may decrease bone mineral density measured at the proximal femur. We did not find evidence to support the use of hormone replacement for osteoporosis in women with primary biliary cirrhosis.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**Hormone replacement versus placebo or no intervention for osteoporosis in women with primary biliary cirrhosis**

**Patient or population:** women with primary biliary cirrhosis.

**Setting:** out-patients.

**Intervention:** hormone replacement versus placebo or no intervention.

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<td>☥️⃝⃝⃝ very low↑.2</td>
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<td>0 per 1000 (0 to 0)</td>
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<td>Study population</td>
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<td>☥️⃝⃝⃝ very low↑.2</td>
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<td>Adverse events</td>
<td>Study population</td>
<td>RR 5.26 (1.26 to 22.04)</td>
<td>49 (2 trials)</td>
<td>☥️⃝⃝⃝ very low↑.2</td>
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<tr>
<td></td>
<td>80 per 1000</td>
<td>421 per 1000 (101 to 1000)</td>
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<td>Change in % of lumbar spine bone mineral density (BMD) per year (g/cm² year⁻¹)</td>
<td>The mean % change of lumbar spine BMD per year in the intervention groups was 1.25 higher (0.91 lower to 3.42 higher)</td>
<td>36 (2 trials)</td>
<td>☥️⃝⃝⃝ very low↑.2</td>
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<td>36 (2 trials)</td>
<td>VERY LOW</td>
<td>1, 2</td>
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*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 The main limitations in design were the lack of clarity of the generation of allocation sequence and blinding in one trial.
2 The included trials in our meta-analysis include few participants and few events indicating that we have little knowledge about the intervention effect, and that further information is needed.
BACKGROUND

Description of the condition

Primary biliary cirrhosis is an autoimmune disease of the liver that primarily affects middle-aged women. They often suffer from post-menopausal osteoporosis due to their age. In addition, primary biliary cirrhosis is associated with metabolic bone disease. Bone loss among patients with primary biliary cirrhosis is twice that of age and sex-matched controls (Eastell 1991), and the prevalence of osteoporosis among these patients is between 14% and 52% (WHO 1994). The precise mechanisms of altered bone homeostasis in primary biliary cirrhosis are unknown, but it seems that osteoclast activity is increased, and in vitro, hyperbilirubinaemia impairs osteoblast function (Hodgson 1993; Janes 1995). Low bone mass is an important cause of morbidity in patients with primary biliary cirrhosis, leading to an increased risk of fractures, pain, and deformity (Rosen 1995).

According to the American Gastroenterological Association guidelines, bone mineral density should be considered in all patients with primary biliary cirrhosis at diagnosis (AGA 2003). The classification of bone mineral density is determined by the standard deviation difference between the patient’s bone mineral density and the mean bone mineral density of a young-adult reference population represented by the T-score (≤ 2.5 'osteoporosis', between 1.0 and 2.5 'low bone mass' or 'osteopenia', and ≥ 1.0 'normal') (WHO 1994). Bone mineral density is measured by dual-energy X-ray absorptiometry, and the result is often reported as 'T-score' (WHO 1994).

Defining optimal treatment regimens for osteoporosis in primary biliary cirrhosis is a challenge as pathogenesis remains poorly understood. Patients with primary biliary cirrhosis are mainly elderly women who are naturally prone to osteoporosis. In general, the principles of management in postmenopausal osteoporosis also apply in primary biliary cirrhosis. Agents shown to be useful in preventing or reducing bone loss in postmenopausal women include calcium, cyclical etidronate, alendronate, risedronate, hormone replacement, raloxifene, calcitonin, and combined vitamin D and calcium (Collier 2002; Wells 2008a; Wells 2008b; Wells 2008c; Arach 2010). Current recommendations are that treatment of osteoporosis should be given for a minimum of five years and bone density repeated after two years and at the end of treatment (Collier 2002). Bisphosphonates should be considered in all patients who have had a fragility fracture or have a T-score below -2.5 (Collier 2002). Bisphosphonates may be used with hormone replacement or without hormone replacement. Calcitriol and calcitonin should be considered in those patients with osteoporosis who are either intolerant of hormone replacement and bisphosphonates, or whose bone mineral density worsens despite the use of bisphosphonates or treatment of hypogonadism (Collier 2002).

Description of the intervention

Hormone replacement generally includes either oestrogen alone or oestrogen combined with progesterone or a chemical analogue, called a progestin. The addition of a progestin reduces the risk of endometrial hyperplasia associated with the use of oestrogen alone in women with a uterus (Lethaby 2004). Progestogens have adverse effects on blood lipids and may cause symptoms such as headache, bloating, and breast tenderness (McKinney 1998). Hormone replacement is used in a variety of formulations which can be taken orally, vaginally, transnasally, as an implant, skin patch, cream, or gel. The transdermal route avoids first-pass metabolism, thus having less metabolic effects on the liver and reducing the cholestatic potential of hormone replacement. Hormone replacement administered transdermally is potentially safer in patients with chronic liver disease (Ribot 1990; Stevenson 1990). Doses often vary cyclically, with oestrogens taken daily and progesterone or progestins taken for about two weeks every month or two. Clinical effects are different according to the type of hormone replacement and its duration of use.

Hormone replacement has been used worldwide to treat symptoms of menopause and to prevent chronic conditions such as osteoporosis. There is no evidence that hormone replacement could prevent cardiovascular events in postmenopausal women (with or without cardiovascular disease) (Gabriel 2005). On the contrary, a Cochrane review assessing the long-term clinical effects of using hormone replacement for perimenopausal and postmenopausal women reports strong evidence that hormone replacement significantly increases the risk of venous thromboembolism, fatal or nonfatal heart attacks (after one year’s use), stroke (after three years use), breast cancer, gallbladder disease, and in women over 65 years, the risk of dementia (Farquhar 2009). Prolonged use of unopposed oestrogen (that is without progesterone) may carry an increased risk for ovarian and endometrial cancer (Rodriguez 2001; Lacey 2002; Riman 2002; U.S. PSTF 2002).

How the intervention might work

Oestrogen has important effects on bone. Oestrogen deficiency is considered to be a major factor leading to bone loss in post-menopausal women. The mechanism of oestrogen effect on bone is via oestrogen receptors that were identified both on osteoclasts and especially on osteoblasts (Lindsay 1993). Oestrogen also has an indirect effect by increasing the production of insulin-like growth factor-1 (IGF-1), insulin-like growth factor-2 (IGF-2), and transforming growth factor-β (TGF-β) which also stimulates bone formation (Wien 1997). Oestrogen replacement reduces bone loss in postmenopausal osteoporosis by inhibiting bone resorption and stimulating new bone formation (Chow 1992; Riggs 1993).

Oestrogen, with or without a progestogen, has beneficial effects on surrogate markers of bone turnover and on fracture risk and has been used extensively for the prevention of osteoporosis. There is
evidence that hormone replacement increases bone mineral density in the hip, lumbar spine, and peripheral body sites (Wells 2002). A meta-analysis of randomised clinical trials has shown that hormone replacement reduces the incidence of non-vertebral fractures in women, but the benefit may decrease if it is started after age of 60 years (Torgerson 2001a). Hormone replacement was associated with significant reduction in vertebral fracture as well (Torgerson 2001b).

Beneficial effects of hormone replacement on bone mineral density in primary biliary cirrhosis have been reported (Olsson 1999; Menon 2003). There is a theoretical concern of worsening cholestasis by application of hormone replacement to patients with primary biliary cirrhosis (Schreiber 1983). However, in a small retrospective study, hormone replacement resulted in a significant increase in bone mineral density compared to untreated patients, and there was no evidence of worsening cholestasis (Crippin 2003). Furthermore, hormone replacement could also be used to treat postmenopausal symptoms in women with primary biliary cirrhosis, and such trials might have examined the effects of hormone replacement on the bone.

Why it is important to do this review

The harms and benefits of hormone replacement for osteoporosis in women with primary biliary cirrhosis are unclear. We could not identify any meta-analyses or systematic reviews that have summarised the evidence in a systematic way.

OBJECTIVES

To assess the beneficial and harmful effects of hormone replacement for osteoporosis in women with primary biliary cirrhosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials irrespective of publication status, language, or blinding, assessing hormone replacement for primary and secondary prevention of osteoporosis in women with primary biliary cirrhosis, were considered for inclusion. For assessment of harm we also considered quasi-randomised and observational studies that came with the search results for randomised clinical trials. We did not perform specific electronic searches for such studies.

Types of participants

Postmenopausal women at any age with primary biliary cirrhosis were included; ie, women having at least two of the following: elevated serum activity of alkaline phosphatases, a positive antimitochondrial antibody, and histologically-proven disease (EASL 2009; AASLD 2010). We included trials in which participants received hormone replacement as primary and secondary prevention. We considered a trial as primary prevention if it included patients that had an average T-score of -1.0 or above, or if the prevalence of vertebral fracture at baseline was less than 20%. We considered a trial as secondary prevention if the inclusion criteria were restricted to patients with T-score between -1 and -2.5 or below -2.5, or to patients who had experienced previous fractures.

Types of interventions

Experimental group: any hormone replacement therapy administered by any route, or regimen, or dose. Control group: no intervention or placebo. Any concomitant interventions were allowed if received equally by all treatment groups in a trial.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Fractures (number of participants with any fracture and number of fractures at all sites).
3. Adverse advents. Serious adverse events were defined as any untoward medical occurrence that resulted in death, were life threatening, or persistent or lead to significant disability; or any medical event which had jeopardised the patient or required intervention to prevent it (ICH-GCP 1997). All other adverse events (that is, any medical occurrence not necessarily having a causal relationship with the treatment, but did, however, caused a dose reduction or discontinuation of the treatment) were considered as non-serious.
4. Quality of life.

Secondary outcomes

1. Bone mineral density measured by dual-energy X-ray absorptiometry:
   - lumbar spine
   - proximal femur
   - hip
   - radius
   - total body.
2. Liver-related mortality or liver transplantation.
3. Liver-related morbidity.
4. Biochemical indices (serum bilirubin, serum alkaline phosphatase, serum alanine aminotransferase, serum aspartate aminotransferase, and albumin).
5. Biochemical markers of bone turnover (serum osteocalcin and the procollagen type I N-terminal propeptide (PINP) - as indices of bone formation, and urinary hydroxyproline and the amino (NTx) and β-carboxyterminal (CTx) telopeptides of collagen I - as indices of bone resorption).
6. Number of patients having hormone replacement withdrawn due to adverse events.

**Search methods for identification of studies**

**Electronic searches**

Relevant randomised clinical trials were identified by electronic searching of the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2011), The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, Science Citation Index Expanded (Royle 2003), LILACS, clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform until November 2011. The search strategies and the time span of the searches are given in Appendix 1.

**Searching other resources**

The reference lists of relevant articles were scanned for additional trials. In order to obtain unpublished trials, the principal authors of the identified clinical trials and pharmaceutical companies involved in the production of oestrogens and progestins were inquired about additional trials they might know of.

**Data collection and analysis**

**Selection of studies**

We listed the identified trials, and two of the authors (JR and GP) independently assessed their fulfilment of the inclusion criteria. Disagreements were resolved by discussion and arbitrated by CG.

**Data extraction and management**

JR and GP extracted data independently using data extraction forms that were developed for the purpose. If information was not available in the published trial, we contacted authors of the trial publications in order to obtain missing data and assess the trials correctly. We added information obtained through correspondence with these authors to the data extraction form. We provided the date for information that was requested and received in the 'Notes' section of the respective trial ('Characteristics of included studies'). Disagreements were resolved by discussion and arbitrated by CG.

From each trial the following information was extracted: first author; country of origin; inclusion and exclusion criteria; number of participants randomised; characteristics of participants: age range (mean or median); trial design; dose of oestrogens and progestins; duration, frequency and mode of administration; type and dose of additional interventions; and outcomes.

**Assessment of risk of bias in included studies**

The confidence that the design and the report of the randomised clinical trial would restrict bias in the comparison of the intervention defines methodological quality defines risk of bias. We have assessed the risk of bias using the following domains (Schulz 1995; Moher 1998; Kjaergard 2001; Gluud 2006; Wood 2008)

- **Random sequence generation (selection bias)**
  - Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent adjudicator.
  - Uncertain risk of bias: the trial was described as randomised, but the method of sequence generation was not specified.
  - High risk of bias: the sequence generation method is not, or may not be, random. Quasi-randomised trials, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

- **Allocation concealment (selection bias)**
  - Low risk of bias: allocation was controlled by a central and independent randomisation unit and the method of sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent adjudicator.
  - High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. Quasi-randomised trials will be excluded for the assessment of benefits but not for harms.

- **Blinding (performance and detection bias)**
  - Low risk of bias: the trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation may have been foreseen in advance of, or during, enrolment.
  - High risk of bias: the method of blinding was described, but the method used to conceal the allocation was not, or may not be, random. Quasi-randomised trials, those using dates, names, or admittance numbers in order to allocate patients are inadequate and will be excluded for the assessment of benefits but not for harms.

- **Incomplete outcome data (attrition bias)**
  - Low risk of bias: the numbers and reasons for dropouts and...
withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Uncertain risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

Selective reporting (reporting bias)
- Low risk of bias: pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
- Uncertain risk of bias: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Other bias
- Low risk of bias: the trial appears to be free of other domains that could put it at risk of bias.
- Uncertain risk of bias: the trial may or may not be free of other domains that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias, eg, for-profit involvement, authors have conducted trials on the same topic etc.

Trials assessed as having ‘low risk of bias’ in all of the specified individual domains were considered ‘trials with low risk of bias’. Trials assessed as having ‘uncertain risk of bias’ or ‘high risk of bias’ in one or more of the specified individual domains were considered trials with ‘high risk of bias’ (Glud 2011).

Assessment of heterogeneity
We explored statistical heterogeneity by the chi-squared test with significance less than or equal to 0.10 and measured the quantity of heterogeneity by I² (Higgins 2003).

Assessment of reporting biases
We intended to use funnel plot graphs in order to inform us of the likelihood of bias in the meta-analysis (Egger 1997; Macaskill 2001). We did not perform a funnel plot as we did not have the recommended minimal number of ten or more trials in any meta-analyses.

Data synthesis
We performed this review according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Glud 2011). For the statistical analyses, we used Review Manager 5 (RevMan 2011). We meta-analysed the data with both a random-effects model (DerSimonian 1986) and a fixed-effect model (DeMets 1987) to ensure robustness of the results. In case of significant differences of the results that the two models produced, we presented the result with both methods. We presented the results with the fixed-effect model if the results of the two models did not differ (Higgins 2002).

Trial sequential analysis
In order to control for the risks of random errors due to sparse data and multiplicity, we performed trial sequential analysis (Brok 2008; Weterslev 2008; Thorlund 2009). We calculated the required information size (ie, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) (Weterslev 2008). The required information size calculation should also account for the diversity present in the meta-analysis (Weterslev 2009). In our analysis, the required information size was based on the minimal relevant difference of a half standard deviation of the meta-analysis, the standard deviation of the meta-
analysis, a type I error of 5%, and a type II error of 20% (Wetterslev 2008). As default, diversity-adjusted required information size was used unless otherwise stated (Wetterslev 2008; Wetterslev 2009). The underlying assumption of trial sequential analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. We added the trials according to the year of publication, and if more than one trial was published in a year, trials were added alphabetically according to the last name of the first author (Wetterslev 2008).

On the basis of the required information size, trial sequential monitoring boundaries were constructed (Wetterslev 2008). These boundaries determine the statistical inference one may draw regarding the cumulative meta-analysis that has not reached the required information size. If the trial sequential monitoring boundary is crossed before the required information size is reached, firm evidence may be established and further trials may turn out to be superfluous. On the other hand, if the boundary is not surpassed, it is most probably necessary to continue doing trials in order to detect or reject a certain intervention effect.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned to be performed to compare:
- trials with low risk of bias compared to trials with high risk of bias;
- different route of administration of hormone replacement;
- different doses of hormone replacement;
- different durations of administration of hormone replacement. Due to the paucity of trials, none of these analyses could be conducted.

RESULTS

Description of studies

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

Results of the search

Our search strategy identified 42 publications, out of which 16 were duplicates. Of the remaining 26 publications, 22 were excluded, either because they were reviews, or because they did not relate to primary biliary cirrhosis, or because they did not describe a randomised clinical trial investigating the effect of hormone replacement in women with primary biliary cirrhosis (Figure 1).
Figure 1. Study flow diagram.

42 records identified through database searching

0 additional records identified through other sources

26 records after duplicates removed

26 records screened

22 records excluded

4 full-text articles assessed for eligibility

2 full-text articles were not a randomised clinical trials

2 trials included in qualitative synthesis

2 trials included in quantitative synthesis
We identified a total of two publications referring to two randomised clinical trials (Characteristics of included studies). The two trials were published as full text articles (Ormarsdottir 2004; Boone 2006). The primary authors were contacted for data and other information on the trials. Dr. Jenny Heathcote kindly responded to our inquiry, but she could not provide data on the trial that had been initiated almost 20 years ago (Boone 2006). No other responses were received.

We contacted manufacturers of oestrogens and progestins and asked for any information about unpublished or on-going trials using oestrogens and progestins involving participants with primary biliary cirrhosis. Novartis, Novo Nordisk, and Noven Pharmaceuticals kindly replied that they knew only of two trials we had already included.

We have not identified any registered ongoing or planned trials through Searching Clinicaltrials.gov (http://clinicaltrials.gov/) and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/).

**Included studies**

We identified and included two randomised clinical trials which assessed the effect of hormone replacement in a total of 49 participants with primary biliary cirrhosis. The trials were conducted in Canada and Sweden. Both trials were multicenter trials with parallel group design (Ormarsdottir 2004; Boone 2006). Hormone replacement versus placebo was assessed in 31 participants in one trial (Boone 2006), and hormone replacement versus no intervention was assessed in 18 participants in another trial (Ormarsdottir 2004). Participants in both trials were postmenopausal women with primary biliary cirrhosis. Those women had previously not been treated with drugs known to affect the bone metabolism. In both trials, hormone replacement was given transdermally. In one trial hormone replacement was given as oestradiol patch in combination with medroxyprogesterone (Ormarsdottir 2004). Oestradiol patch was given in a dose of 50 µg per day twice weekly, and medroxyprogesterone in a dose of 2.5 mg daily continuously (if more then 2 years from menopause), or in a dose of 10 mg daily for 12 days per month (if less then 2 years from menopause) (Ormarsdottir 2004). In the other trial, hormone replacement was given as 7β-estradiol for two weeks followed by two weeks of combined transdermal norethisterone acetate and 17β-estradiol (Boone 2006). 7β-estradiol was given in a dose of 0.05 mg daily and norethisterone acetate in a dose of 0.25 mg daily. The duration of administration of hormone replacement was two years in both trials. All patients received vitamin D and calcium. In one trial, vitamin D was given in a dose of 0.25 µg daily, and calcium in a dose of 1 g daily (Ormarsdottir 2004). In the other trial, vitamin D was given in a dose of 1000 IU daily, and calcium in a dose of 1500 mg daily (Boone 2006). Both trials reported similar outcome measures: bone mineral density measured at the lumbar spine and proximal femur, clinical events, fractures, changes in biochemical variables, and adverse events.

**Excluded studies**

We excluded two studies because they were not randomised clinical trials (Menon 2003; Pereira 2004) (Characteristics of excluded studies).

**Risk of bias in included studies**

Risk of bias was assessed according to six domains: sequence generation; allocation concealment; blinding; handling of incomplete outcome data; selective outcome reporting; and other potential sources of bias. One was assessed as having a low risk of bias (Boone 2006), and the other as having a high risk of bias (Ormarsdottir 2004) (Figure 2). Statistical analyses, which include both trials, are, therefore, based on trials with high risk of bias (Figure 3; Summary of findings for the main comparison).
Figure 2. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.
**Allocation**

In the trial assessing hormone replacement versus placebo, sequence generation was achieved using a randomisation table (Boone 2006). The method of sequence generation was not specified. In the trial assessing hormone replacement versus no intervention (Ormarsdottir 2004), allocation concealment was performed by independent pharmacist who had no role in patient contact or follow-up, nor did he/she participate in data analysis (Boone 2006) and control by sealed envelopes (Ormarsdottir 2004).

**Blinding**

One trial was blinded (Boone 2006). The other trial did not report on blinding and was likely unblinded (Ormarsdottir 2004).

**Incomplete outcome data**

The numbers and reasons for dropouts and withdrawals in all intervention groups were described in both included trials.

**Selective reporting**

The protocols were not available for any of the trials, but predefined, or clinically relevant and reasonably expected outcomes were reported.

**Other potential sources of bias**

The trial assessing hormone replacement versus placebo seems to be free from other potential sources of bias, apart from the fact that it reported that transdermal oestrogen/progestin and placebo were supplied by Novartis (Boone 2006). Novartis was not involved in the collection, analysis, or presentation of the data (Boone 2006). The trial assessing hormone replacement versus no intervention reported sponsorship from Novartis, but it did not report if Novartis was involved in the collection and data analysis in presentation of the results (Ormarsdottir 2004).

**Effects of interventions**

See: Summary of findings for the main comparison Hormone replacement versus placebo or no intervention for osteoporosis in women with primary biliary cirrhosis

See Summary of findings for the main comparison.

**Primary outcomes**

**All-cause mortality**

No deaths were reported for any of the two groups (0/24 versus 0/25 participants) (RD 0.00; 95% CI -0.11 to 0.11; I² = 0%) (Analysis 1.1).

**New fractures**

In the trial assessing hormone replacement versus no intervention, no fractures were found in either groups (Ormarsdottir 2004). In the trial assessing hormone replacement versus placebo, 2/15 participants in the placebo group reported fractures compared with 0/16 participants in the treatment group (Boone 2006). There was no statistically significant difference in the number of participants with new fractures in the treatment group compared with controls (RD -0.08; 95% CI -0.24 to 0.07; I² = 0%) (Analysis 1.2).

**Adverse events**

There was a statistically significant increase in the occurrence of adverse events in the hormone replacement group (10/24) versus the control group (2/25) (RR 5.26; 95% CI 1.26 to 22.04; I² =
0% (Analysis 1.3). Reasons for withdrawal of participants due to the occurrence of adverse events are provided in Table 1 and Table 2.

For assessment of harm, besides the data provided by the two randomised trials (Ormsardottir 2004; Boone 2006) (Table 1; Table 2) we also considered the data from two non-randomised studies which reported on harm (Menon 2003; Pereira 2004). In Menon 2003, in the hormone replacement group, there were 6 patients out of 46 who experienced adverse events versus 0 patients out of 46 in the control group (Table 3). In Pereira 2004, in the hormone replacement group, there were 2 patients out of 21 who experienced an adverse event versus 0 patients out of 21 in the control group (Table 4).

Quality of life
No quality of life measurements were reported.

Secondary outcomes
Change in per cent in bone mineral density per year (g/cm² year⁻¹)
Hormone replacement had no significant effect on bone mineral density measured at the lumbar spine compared with placebo or no intervention (MD 1.25 g/cm² year⁻¹; 95% CI -0.91 to 3.42; I² = 0%) (Analysis 1.4). Hormone replacement seemed to significantly decrease bone mineral density at the proximal femur (MD 2.24 g/cm² year⁻¹; 95% CI 0.74 to 3.74; I² = 0%) (Analysis 1.5). Trial sequential analysis on data for bone mineral density at the proximal femur does not support the findings in Analysis 1.5. The cumulated Z-curve (blue curve) did not cross the trial sequential monitoring boundary (red curve) implying that there is no firm evidence that hormone replacement decreases bone mineral density measured at proximal femur (Figure 4).
Figure 4. Trial sequential analysis of the cumulative meta-analysis of the effect of hormone replacement versus control on bone mineral density measured at proximal femur in women with primary biliary cirrhosis. The diversity-adjusted required information size (DARIS) of 130 patients is calculated based on a minimal relevant intervention effect (MIREDIF) of 1.6 g/cm²/year, a standard deviation of 3.2 g/cm²/year, a risk of type 1 error of 5%, a power of 80%, and a diversity of 0%. The cumulated Z-curve (blue curve) did not cross the trial sequential monitoring boundary (red curve) implying that there is no firm evidence for an effect of 1.6 g/cm²/year decrease in bone mineral density measured at proximal femur when the cumulative meta-analysis is adjusted for sparse data and multiple testing on accumulating data.

Liver-related mortality or liver transplantation
Hormone replacement had no significant effect on liver-related mortality or liver transplantation. There were no liver-related deaths reported for any of the two groups (0/24 versus 0/25 participants) (RD 0.00; 95% CI -0.11 to 0.11; I² = 0%) (Analysis 1.6).

Liver-related morbidity
Hormone replacement did not seem to have significant effect on liver-related morbidity. Liver-related complications occurred in 1/24 participants in the hormone replacement group versus 1/25 participants in the control group (RR 1.07; 95% CI 0.15 to 7.63; I² = 0%) (Analysis 1.7). One woman in the control group had an increase in bilirubin after twelve months (> 100% increase from baseline) and developed ascites afterwards in the following six months (Ormarsdottir 2004). One women in the treatment group experienced two episodes of variceal haemorrhage (at months 4 and 17 of the trial period) requiring hospital admission, blood transfusion, and band ligation.

Biochemical indices
Two trials reported on serum bilirubin concentration. In one trial the data were reported as percentage change from baseline presented as median with ranges, and in addition they provided the table with final values presented as median with ranges (Ormarsdottir 2004). We used only data presented as final values.
In another trial, the data were reported as final values presented as means with ranges (Boone 2006). In order to perform our meta-analysis, we estimated standard deviation to be approximately one quarter of the typical range of data values (Higgins 2011). In fixed-effect meta-analysis, hormone replacement versus placebo or no intervention had no significant effect on serum bilirubin concentration (MD 4.60 μmol/L; 95% CI -3.42 to 12.62; I² = 0%) (Analysis 1.8).

One trial reported that the relative change of serum alkaline phosphatases, serum alanine aminotransferase, and albumin concentration over baseline values did not differ when the two treatment groups were compared (Ormardottir 2004). The data were reported as percentage change from baseline presented as median with ranges (Table 5).

No trial reported on serum aspartate aminotransferase activity and biochemical markers of bone turnover.

**Number of patients having hormone replacement withdrawn due to adverse events**

There was a statistically significant increase in the number of patients having hormone replacement withdrawn due to adverse events in the hormone replacement group (10/24) versus the control group (2/25) (RR 5.26; 95% CI 1.26 to 22.04, I² = 0%) (Analysis 1.9). Reasons for withdrawal of participants due to the occurrence of adverse events are provided in Table 2 and Table 1.

**Subgroup analyses**

It was not possible to perform the planned subgroup analyses due to the paucity of trials.

**DISCUSSION**

**Summary of main results**

Hormone replacement had no significant effect on mortality and fractures compared with placebo or no intervention in women with primary biliary cirrhosis. It seems that hormone replacement given to women with primary biliary cirrhosis is connected with a significant increase in the occurrence of adverse events compared with placebo or no intervention. It was not possible to evaluate changes in quality of life since none of the trials reported this variable.

Hormone replacement had no significant effect on lumbar bone mineral density measured by dual-energy X-ray absorptiometry compared with placebo or no intervention. Hormone replacement seemed to significantly decrease bone mineral density measured at the proximal femur compared with the control. However, this finding was not supported by trial sequential analysis. Hormone replacement had no significant effect on liver-related mortality or liver transplantation, and liver-related morbidity compared with placebo or no intervention in women with primary biliary cirrhosis. It seems that hormone replacement had no significant effect on serum bilirubin concentration compared with placebo or no intervention. However, the data are scarce, and we cannot exclude substantial risks of type II errors.

**Overall completeness and applicability of evidence**

This systematic review examined the evidence from two included randomised clinical trials for the use of hormone replacement for osteoporosis in women with primary biliary cirrhosis. We could not obtain all relevant data regarding all reasonably expected outcomes, as the identified trials addressed insufficiently all of the objectives of our review.

The two trials assessing hormone replacement versus placebo or no intervention reported on mortality and fractures, and the results were inconclusive. The lack of significant differences in mortality or fractures may be related to the small number of participants involved and the short duration of the trials.

During the recruitment phase of the two trials, a large percentage of women declined to participate in the trials. In one trial, it was reported that 66% of women declined to participate for a variety of reasons, including worry over a family history of breast cancer. Even though there is evidence that hormone replacement increases bone mineral density (Wells 2002) and reduces the incidence of vertebral and non-vertebral fractures (Torgerson 2001a; Torgerson 2001b) in postmenopausal women, there is an increasing concern about the adverse events of hormone replacement among women. Apart from the fact that oestrogen deficiency is considered to be a major factor leading to bone loss in postmenopausal women, there is strong evidence that hormone replacement significantly increases the risk of venous thromboembolism, heart attack, stroke, breast cancer, gallbladder disease, and in women over 65 years, the risk of dementia (Farquhar 2009).

Regarding safety of hormone replacement in women with primary biliary cirrhosis, we found statistically significant difference in the occurrence of adverse events between the treatment and control groups. It seems that hormone replacement given to women with primary biliary cirrhosis is connected with a significant increase in the occurrence of adverse events compared with placebo or no intervention. When participants are aware of the treatment they are receiving, they may be more or less likely to report adverse events. The judgment of individuals who collect and interpret patient data may be affected when the assessor is aware of the treatment a participant is receiving. Lack of blinding in one trial out of the two in total that reported on adverse events may result in biased results.

There is a theoretical concern of worsening cholestasis by application of hormone replacement to patients with primary biliary cirrhosis (Schreiber 1983). Both included trials reported on serum bilirubin concentration to reflect their concern of possible worsening of cholestasis by application of hormone replacement to women with primary biliary cirrhosis. These data were reported using ranges rather than standard deviations, and we considered...
this as an indicator that the outcome distribution in trials is possibly skewed. Even though ranges should not be used to estimate the standard deviation, we used an approach which estimates the standard deviation to be approximately one quarter of the typical range of data values. Accordingly, the result of our meta-analysis for this outcome is not a robust result, and we cannot conclude that hormone replacement influences serum bilirubin concentration in women with primary biliary cirrhosis.

**Quality of the evidence**

We conducted this review according to *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2011). The results of our meta-analysis, however, are only as strong as the primary trials included.

The main limitations in the design and implementation were fracture assessment and classification, the lack of clarity of the generation of allocation sequence and blinding in one trial, and the small number of participants enrolled in the trials. We explored the presence of statistical heterogeneity by the chi-squared test and measured the quantity of heterogeneity by $I^2$ (Higgins 2003). Chi-squared tests have low power in the situation of a meta-analysis when trials have small sample sizes or are few in number as our included trials are. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. There was no significant intertrial heterogeneity for any outcome measure. We analysed our data with both fixed- and random-effects models. In case of significant differences of the results produced by the two models, we presented the result with both methods.

Our results are imprecise as included trials in our meta-analysis include few participants and few events and thus have wide confidence intervals around the estimate of effect. Furthermore, we may elicit suspicion of publication bias as the included trials are small. Both trials reported industrial sponsorship from Novartis which was not involved in the data collection, analysis, or presentation in one trial, and in the other trial it was unclear if Novartis was involved in the collection and analysis of the data presentation of the results.

**Potential biases in the review process**

In this systematic review, a comprehensive literature search was performed, inclusion and exclusion criteria were specified, and data analyses were conducted. A potential limitation of our approach may be that we have not specifically searched for trials in grey literature so this may have introduced a slight risk of bias into our meta-analyses (Egger 2003). This bias, however, is unlikely to influence our results as grey literature trials report seldom beneficial effects.

Risk of bias is known to have impact on the estimated intervention effect; trials with high risk of bias tend to overestimate the beneficial intervention effect (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008). From the two included trials, adequate allocation sequence generation was reported in one trial, adequate allocation concealment in two trials, one trial was blinded, both trials adequately addressed incomplete data and reported on clinically relevant and reasonably expected outcomes, and one trial appeared to be free of other domains that could put it at risk of bias. Accordingly, one trial was adequate regarding all domains. Therefore, the estimated intervention effect for all outcome measures that was calculated using data from the two included trials is at high risk of bias. This is not a robust result, so the observed intervention effect may be due to systematic error.

A limitation of this review is also that both included trials had a small sample size, with an average of 25 women with primary biliary cirrhosis. Small trials have less power, meaning that there is less chance of detecting a small but true effect as statistically significant (Kjaergard 2001). The risk of random error is higher when data come from small sample sizes for individual trials, so information sizes in a meta-analysis need to be sufficiently large in order to reduce the risk of random error and increase the chance of observing a true intervention effect (Brok 2008; Weterslev 2008). This is one reason for also analysing the data with trial sequential analysis.

**Agreements and disagreements with other studies or reviews**

We could not compare our results with the results from other systematic reviews or meta-analysis, as we could not identify any meta-analyses or systematic reviews assessing hormone replacement for osteoporosis in patients with primary biliary cirrhosis that have summarised the available evidence in a systematic way.

**Authors’ Conclusions**

**Implications for practice**

Treatment of osteoporosis in women with primary biliary cirrhosis with hormone replacement cannot be supported based on the available evidence.

We found no evidence of effect of hormone replacement on mortality and fractures in women with primary biliary cirrhosis. This lack of effect may be due to the small number of included trials with small number of participants. It seems that hormone replacement given to women with primary biliary cirrhosis is connected with a significant increase in the occurrence of adverse events compared with placebo or no intervention. In women with primary biliary cirrhosis, hormone replacement appears to have no effect on the lumbar bone mineral density measured by dual-energy X-
ray absorptiometry compared with placebo or no intervention. Hormone replacement may decrease bone mineral density at the proximal femur. It seems that hormone replacement has no significant effect on liver-related mortality or liver transplantation, liver-related morbidity, and serum bilirubin concentration compared with placebo or no intervention, but absence of evidence for these effects is not evidence of absence of such effects.

Implications for research
Randomised clinical trials which assess hormone replacement in primary biliary cirrhosis with larger sample sizes and varying degrees of osteoporosis, and minimised risk of bias are needed. Multi-centre trials would be appropriate for participant recruitment as primary biliary cirrhosis is a relatively rare disease. Such trials ought to be reported according to the CONSORT guidelines (http://www.consort-statement.org/).

Acknowledgements
We thank the patients who entered the trials and the investigators who conducted them. We also thank Dr. Jenny Heathcote who kindly responded to our request for further information on the trial she was involved in. We thank Dimitrinka Nikolova, The Cochrane Hepato-Biliary Group, for expert assistance during the preparation of this review and excellent collaboration. Also, we are very grateful to Sarah Louise Klingenberg, The Cochrane Hepato-Biliary Group, for her contribution with searches for this review. Joseph C. Jones and Shahida Hasan from Noven Pharmaceuticals, Inc., Kasper Højby Nielsen from Novo Nordisk A/S, and Jean Desforges and Kirtida Pandya from Novartis are thanked for reply on no knowledge of further trials.

Protocol:
Peer Reviewers: Jane R. Campos, the Philippines; Luit Penninga, Denmark; Sei Kakinuma, Japan.

Contact Editor: Rosa Simonetti, Italy.

Review:
Peer Reviewers: Martin Prince, UK; Julia Newton, UK; M Conchillo, Spain.

Contact Editor: Rosa Simonetti, Italy.

References

References to studies included in this review
Boone 2006 {published data only}

Ormarsdottir 2004 {published data only}

References to studies excluded from this review
Menon 2003 {published data only}

Pereira 2004 {published data only}

Additional references
AASLD 2010

AGA 2003

Arteh 2010

Brok 2008

Chow 1992
Chow J, Tobias JH, Colston KW, Chambers TJ. Estrogen maintains trabecular bone volume in rats not only by suppression of bone resorption but also by stimulation of

**Collier 2002**

**Crippin 2003**

**DeMets 1987**

**DerSimonian 1998**

**EASL 2009**

**Eastell 1991**

**Egger 1997**

**Egger 2003**

**Farquhar 2009**

**Gabriel 2005**

**Gluud 2006**

**Gluud 2011**

**Higgins 2002**

**Higgins 2003**

**Higgins 2011**

**Hodgson 1993**

**Hollis 1999**

**ICH-GCP 1997**

**Janes 1993**

**Kjaergard 2001**

**Lacey 2002**

**Lethaby 2004**
Lindsay 1993

Macaskill 2001

McKinney 1998

Moher 1998

Olsson 1999

RevMan 2011

Riggs 1993

Riman 2002

Rodriguez 2001

Rosen 1995

Royle 2003

Wells 2008c

Wetterslev 2008

Wetterslev 2009

WHO 1994

Wood 2008

Wren 1997

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

**Ormarsdottir 2004**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Methods**     | Multicentre randomised clinical trial with parallel group design (two interventions groups).  
Trial duration: two years. |
| **Participants**| Country: Sweden.  
Number of participants randomised: 18, median age 57 years.  
Inclusion criteria:  
- postmenopausal women between the age of 40 and 70 years with the diagnosis of primary biliary cirrhosis (presence of anti-mitochondrial antibodies and liver histopathology compatible with primary biliary cirrhosis), and Child-Pugh score A  
* postmenopausal status was defined as loss of menstruations for at least one year and elevated follicle-stimulating hormone compatible with a postmenopausal status  
Exclusion criteria:  
- other bone disorders than osteoporosis related to liver disease or postmenopausal status;  
- history of cancer;  
- unexplained vaginal bleeding;  
- unexplained uterus enlargement or lump in the breasts;  
- history of thromboembolic disorder;  
- hyperthyroidism;  
- impairment of the renal function;  
- severe heart disease;  
- uncontrolled hypertension (diastolic blood pressure > 100 mmHg);  
- history of drug or alcohol abuse;  
- treatment with calcitonin, high-dose vitamin D (more than 50,000 IU weekly), systemic corticosteroids, high dose heparin, oestrogen (except for local preparations not containing oestradiol), progestagens, fluorides, or bisphosphonates |
| **Interventions**| Participants were randomly assigned to receive:  
Intervention group 1: transdermal hormone replacement (oestradiol patch, 50 µg per day twice weekly in combination with medroxyprogesterone), n = 8. Duration of administration of hormone replacement was two years.  
Intervention group 2: no hormone replacement, n = 10.  
A dose for medroxyprogesterone was 2.5 mg daily continuously if more than two years from menopause, and 10 mg daily for 12 days per month if less than two years from menopause  
All patients received vitamin D (alfacalcidol) 0.25 µg daily and calcium 1 g daily |
| **Outcomes**    | Outcome measure(s):  
- bone mineral density of the lumbar spine and proximal femur;  
- fractures;  
- biochemical variables (serum bilirubin, liver enzymes, albumin);  
- adverse events. |
| **Notes**       | Additional information requested on 18th March 2011, but no response was received. |
### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>The trial is described as randomised, but the method of sequence generation was not specified</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation was controlled by sealed envelopes so that intervention allocation could not have been foreseen in advance of, or during enrolment</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>The trial did not discuss this domain and was likely unblinded</td>
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<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>The numbers and reasons for dropouts and withdrawals in all intervention groups were described</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Pre-defined, or clinically relevant and reasonably expected outcomes are reported on</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>The trial reported sponsorship from Novartis, but it did not report if Novartis was involved in the collection and analysis of the data</td>
</tr>
</tbody>
</table>

### Boone 2006

#### Methods
Multicentre randomised clinical trial with parallel group design (two interventions groups).
Trial duration: two years.

#### Participants
Country: Canada.
Number of participants randomised: 31, mean age 55 years.
Inclusion criteria:
- postmenopausal women ≤ 65 years with primary biliary cirrhosis (alkaline phosphatases > 110 U/L, positive anti-mitochondrial antibody, and/or compatible liver biopsy)
- postmenopausal status was defined as no menstrual periods for at least six consecutive months, or a hysterectomy with conservation of at least one ovary and the typical symptoms of oestrogen deficiency, and an elevated follicle-stimulating hormone in the postmenopausal range (> 34.4 IU/L);
- a normal pelvic examination, normal Papanicolaou test, and breast examination;
- haemoglobin > 80 mg/L;
- voluntary informed consent.
Exclusion criteria:
- patients who did not meet the inclusion criteria;
- a liver transplanted patients;
- serum bilirubin > 120 µmol/L;
- current treatment with oestrogen or progestin (or patients that had received treatment for more then six months since the onset of menopause);
- vitamin D deficiency;
- contraindications to oestrogen use;
- treatment with drugs known to affect bone metabolism;
- other chronic disease affecting bone metabolism;
- severe spinal deformities that would preclude accurate BMD measurement;
- patients that had been immobile for more then three months in the preceding year;
- allergy to components of the patch or bandages.

Interventions

Participants were randomly assigned to receive:
Intervention group 1: 17β-estradiol (0.05 mg daily) for 14 days followed by 14 days of combined transdermal norethisterone acetate (0.25 mg daily) and 17β-estradiol (0.05 mg daily) transdermally, n = 16. Duration of administration of hormone replacement was two years.
Intervention group 2: identical placebo patches applied in the same manner, dose, and frequency, n = 15.
All patients received vitamin D 1000 IU daily and elemental calcium 1500 mg daily.

Outcomes

Outcome measure(s):
- clinical variables;
- fractures;
- bone mineral density of the lumbar spine and proximal femur;
- measurements of biochemical markers of bone turnover (bone alkaline phosphatases and the amino telopeptides of collagen I);
- biochemical variables (serum bilirubin, liver enzymes, lipid profile, prothrombin time, etc);
- adverse events.

Notes

Additional information requested on 21st March 2011. Dr. Jenny Heathcote kindly responded on 24th March but she could not provide data on the trial that had been initiated almost 20 years ago.

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Sequence generation was achieved using randomisation table.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Allocation was performed by independent pharmacist who had no role in patient contact or follow-up, nor did he/she participate in data analysis, so the intervention allocation could not have been foreseen in advance of, or during enrolment</td>
</tr>
</tbody>
</table>
Boone 2006 (Continued)

| Blinding (performance bias and detection bias) | Low risk | The trial was described as blinded, the parties that were blinded, and the method of blinding was described, so that knowledge of allocation was adequately prevented during the trial |
| Incomplete outcome data (attrition bias) | Low risk | The numbers and reasons for dropouts and withdrawals in all intervention groups were described |
| Selective reporting (reporting bias) | Low risk | Pre-defined, or clinically relevant and reasonably expected outcomes are reported on |
| Other bias | Low risk | The trial seems to be free from other potential sources of bias. The trial reported that transdermal oestrogen/progestin and placebo were supplied by Novartis, and that Novartis was not involved in the collection, analysis, or presentation of these data |

> = greater than or equal to

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menon 2003</td>
<td>Not a randomised clinical trial. The aim of this study was to determine the safety and the efficacy of oestrogen replacement therapy in postmenopausal women with primary biliary cirrhosis Forty-six unselected postmenopausal women with primary biliary cirrhosis receiving oestrogens for at least six months before inclusion in this study were randomly matched for age, gender, and ethnic group with another patient with primary biliary cirrhosis but not receiving oestrogen therapy. All patients were taking ursodeoxycholic acid (13 to 15 mg/kg/day) during the study. Thirty-five women were taking estrogens alone, and 11 women were taking a combined oestrogen/progesterone regimen. Twenty-one women were receiving oral replacement therapy, 23 topical replacement therapy, and two women long-acting parenteral therapy</td>
</tr>
<tr>
<td>Pereira 2004</td>
<td>Not a randomised clinical trial. Forty-two post-menopausal women with primary biliary cirrhosis were treated with calcium and vitamin D. They could choose to receive it either alone (n = 21) or together with transdermal hormone replacement therapy (n = 21). The two groups were well matched for age, duration of menopause (mean, 10.7 years; range, 1 to 26 years), body mass index (mean, 24.2 kg/m2; range, 17.3 to 31.8 kg/m2), histological stage, serum bilirubin level (mean, 16.9 lm; range, 4 to 65 lm) and Mayo Clinic R score (mean, 3.3; range, 1.0 to 4.6) There were no adverse events attributable to treatment, apart from two patients who stopped HRT because of monthly...</td>
</tr>
</tbody>
</table>
Continued

bleeding and declined continuous combination therapy

HRT = hormone replacement therapy.
### DATA AND ANALYSES

**Comparison 1. Hormone replacement versus placebo or no intervention**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 All-cause mortality</td>
<td>2</td>
<td>49</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.0 [-0.11, 0.11]</td>
</tr>
<tr>
<td>2 Fractures</td>
<td>2</td>
<td>49</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>-0.08 [-0.24, 0.07]</td>
</tr>
<tr>
<td>3 Adverse events</td>
<td>2</td>
<td>49</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.26 [1.26, 22.04]</td>
</tr>
<tr>
<td>4 Change in % of lumbar spine bone mineral density (BMD) per year (g/cm²/year⁻¹)</td>
<td>2</td>
<td>36</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>1.25 [-0.91, 3.42]</td>
</tr>
<tr>
<td>5 Change in % of proximal femur bone mineral density (BMD) per year (g/cm²/year⁻¹)</td>
<td>2</td>
<td>36</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>2.24 [0.74, 3.74]</td>
</tr>
<tr>
<td>6 Liver-related mortality or liver transplantation</td>
<td>2</td>
<td>49</td>
<td>Risk Difference (M-H, Fixed, 95% CI)</td>
<td>0.0 [-0.11, 0.11]</td>
</tr>
<tr>
<td>7 Liver-related morbidity</td>
<td>2</td>
<td>49</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.07 [0.15, 7.63]</td>
</tr>
<tr>
<td>8 Bilirubin (µmol/L)</td>
<td>2</td>
<td>36</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>4.60 [-3.42, 12.62]</td>
</tr>
<tr>
<td>9 Number of patients having hormone replacement withdrawn due to adverse events</td>
<td>2</td>
<td>49</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.26 [1.26, 22.04]</td>
</tr>
</tbody>
</table>

### ADDITIONAL TABLES

**Table 1. Reasons for withdrawals from treatment due to adverse events (Ormarsdottir 2004)**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Hormone replacement</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary spotty vaginal bleeding</td>
<td>1/8</td>
<td>0/10</td>
</tr>
<tr>
<td>Slight increase in systolic blood pressure</td>
<td>1/8</td>
<td>0/10</td>
</tr>
<tr>
<td>Increase in liver enzymes</td>
<td>1/8</td>
<td>0/10</td>
</tr>
<tr>
<td>Increase in bilirubin concentration</td>
<td>0/8</td>
<td>1/10</td>
</tr>
</tbody>
</table>
Table 2. Reasons for withdrawals from treatment due to adverse events (Boone 2006)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Hormone replacement</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised pruritus</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Pneumonia, pulmonary embolism</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Abdominal pain, headache</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Local pruritus at patch site</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Heavy vaginal bleeding</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Breast pain, chest pain, generalised pruritus, dysuria</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Local pruritus at patch site</td>
<td>1/16</td>
<td>0/15</td>
</tr>
<tr>
<td>Diffuse painful rash of lower back</td>
<td>0/16</td>
<td>1/15</td>
</tr>
</tbody>
</table>

Table 3. Adverse events (Menon 2003)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Hormone replacement</th>
<th>No intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast tenderness</td>
<td>1/46</td>
<td>0/46</td>
</tr>
<tr>
<td>Vaginal spotting</td>
<td>1/46</td>
<td>0/46</td>
</tr>
<tr>
<td>Increase in bilirubin concentration</td>
<td>4*/46</td>
<td>0/46</td>
</tr>
</tbody>
</table>

*In three of the four patients with increase in bilirubin concentration, this was because of worsening liver function, as manifest by worsening ascites and development of oesophageal varices. The remaining patient developed elevations in her serum bilirubin and alkaline phosphatase after stopping ursodeoxycholic acid therapy.

Table 4. Adverse events (Pereira 2004)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Hormone replacement patches</th>
<th>No intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monthly bleeding</td>
<td>2/21</td>
<td>0/21</td>
</tr>
</tbody>
</table>
Table 5. Biochemical indices (Ormarsdottir 2004)

<table>
<thead>
<tr>
<th>Outcome measure (maximum change % from baseline value)</th>
<th>Type of data</th>
<th>Oestrogen + vitD + Ca (median(range))</th>
<th>vitD + Ca (median(range))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum alkaline phosphatases (µkat/L)</td>
<td>Continuous</td>
<td>-4 (-34 to 29)</td>
<td>-2 (-10 to 35)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum alanine aminotransferase (µkat/L)</td>
<td>Continuous</td>
<td>-5 (-24 to 483)</td>
<td>8 (-7 to 140)</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>Continuous</td>
<td>-5 (-12 to 0)</td>
<td>-5 (-14 to 5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

µkat/L = 60 U/L.

**HISTORY**


Review first published: Issue 12, 2011

**CONTRIBUTIONS OF AUTHORS**

JR, GP, MK, GB, and CG were involved in the study concept and design.

JR and GP screened the literature, selected publications for inclusion and exclusion according to the eligibility criteria, extracted data, and made the risk of bias judgements.

JR, GB, and CG analysed and interpreted the data and results.

JR drafted the manuscript and performed the meta-analyses.

MK, GB, and CG were involved in critical revision of the manuscript for important intellectual content.

**DECLARATIONS OF INTEREST**

None known.
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Internal sources
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External sources
- Clinic of Gastroenterology, Clinical Centre of Serbia, Belgrade, Serbia.
- Ministry of Science (Grant No. 41004), Serbia.