Effect on bone health of estrogen preparations in premenopausal women with anorexia nervosa: a systematic review and meta-analyses

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CRD summary
The authors concluded that there was insufficient evidence on the effects of oestrogen preparations on bone mineral density and bone fracture risk in women with anorexia nervosa and that most women with anorexia should avoid using oestrogen preparations. Overall, the authors conclusions reflect the limited evidence presented and their cautious conclusions and recommendations seem appropriate.

Authors' objectives
To evaluate the effect of oestrogen preparations on bone mineral density and bone fracture risk in women with anorexia nervosa.

Searching
MEDLINE, EMBASE, Cochrane CENTRAL, Scopus and Web of Science were searched from inception to March 2008 for publications in any language. Reference sections of pertinent reviews and eligible studies were checked for additional references.

Study selection
Prospective cohort studies and randomised controlled trials (RCTs) in premenopausal women aged 12 to 45 years with anorexia nervosa were eligible for inclusion. Studies had to compare the effectiveness of oestrogen preparations (with or without progestins) used for at least six months to any control intervention on bone fractures or bone mineral density (measured using eligible scanning technologies, as stated in the review). Studies of perimenopausal and postmenopausal women, women without a uterus or with premature ovarian failure and studies in which most women did not have amenorrhoea were excluded.

Most of the women who enrolled were young (median age 17.6 years). Mean durations of amenorrhoea ranged from 4.15 to 22.4 months. Body mass index values for patients ranged from 15.0 to 18.8 (median value 17.9). All but one of the studies assessed bone mineral density using dual x-ray absorptiometry of the lumbar spine and femoral neck (some also measured the total body); the other study estimated bone mineral density using spinal computerised tomography. The oestrogen treatments in most studies were oral contraceptives (25 to 35 μg of ethinyl estradiol); one study administered a combination of premarin (0.625mg) and provera (5mg). Control treatments included placebos, no medication and dehydroepiandrosterone (DHEA).

Two reviewers independently selected the studies for inclusion in the review; any disagreements were resolved by consensus or referral to a third reviewer.

Assessment of study quality
Two reviewers independently assessed methodological quality of included RCTs in terms of allocation concealment and blinding of patients, health care providers and outcome assessors. The Newcastle-Ottawa scale was used to assess cohort studies, according to criteria on representativeness of exposed and nonexposed cohorts, ascertainment of exposure, comparability of cohorts, bias in outcome assessment and adequacy of follow-up.

Data extraction
Two reviewers independently extracted baseline and final assessment data on bone fractures and bone mineral density to calculate, where possible, mean changes from baseline and their 95% confidence intervals (CI). Authors were contacted for any missing data.

Methods of synthesis
Pooled mean changes from baseline and corresponding 95% confidence intervals were calculated using DerSimonian and Laird random-effects models. Statistical inconsistency was assessed using the $I^2$ statistic ($I^2<25\%$ indicated small
inconsistency and $I^2 > 50\%$ indicated large inconsistency across studies).

Subgroup analyses were conducted to assess the effects of variables on the results (reported further in the review).

**Results of the review**

Six studies (385 participants) were included in the review: four RCTs (315 participants) and two cohort studies (70 participants). Duration of follow-up ranged between nine and 18 months. Loss to follow-up ranged from 8.3\% to 27.6\% in the RCTs and from 6.25\% to 14\% in the cohort studies. Two of the four RCTs reported adequate blinding of participants, health care providers and outcome assessors. Further quality assessment results (including those for the cohort studies) were reported in the review.

Oestrogen preparations statistically significantly reduced loss of bone mineral density at the lumbar spine compared to control treatments (mean change from baseline 0.33, 95\% CI 0.09 to 0.56; $I^2 = 0\%$; four RCTs, two cohort studies). No statistically significant difference was found between the treatments when bone mineral density loss was measured at the femoral neck (mean change from baseline 0.13, 95\% CI -0.16 to 0.43; $I^2 = 0\%$; three RCTs, one cohort study).

One RCT reported on bone fractures; there were two fractures but it was unclear in which treatment groups the fractures occurred. No differences were observed in any of the subgroup analyses.

Other results (including from five studies identified post hoc) were reported in the review.

**Authors' conclusions**

The evidence is of low quality and offers weak inferences regarding the clinical efficacy of oestrogen preparation use on bone mineral density and bone fracture risk, particularly in women with anorexia nervosa and amenorrhoea.

**CRD commentary**

The review addressed a clear question and criteria for inclusion of studies in the review were stipulated. Appropriate electronic databases were searched. There was no attempt to identify unpublished studies so there was a risk of publication bias (acknowledged by the authors). Steps were taken to minimise errors and bias at all stages of the review process.

Pooling of randomised and non-randomised studies may not be appropriate because the results of non-randomised studies are associated with potential biases. Only a small number of studies were identified and included in the review. The authors acknowledged that the subgroup analyses were underpowered. They also acknowledged some of the methodological limitations of the RCTs.

The evidence base was small but the findings were generally consistent. Overall, the authors conclusions reflect the evidence presented and their cautious conclusions and recommendations seem appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that decisions about oestrogen preparations in women with anorexia nervosa require careful consideration of patient preferences and the benefits associated with oestrogen preparations. The authors recommended against use of oestrogen preparations in the vast majority of women with anorexia. The authors stated that the findings may not be generalisable to non-white non-European ethnic groups.

**Research:** The authors stated that large, long-term, rigorous trials in women with anorexia nervosa and that use standardised methods were needed to provide stronger evidence. Data should be collected on clinical fragility fractures because that would provide a more clinically meaningful outcome to patients. Researchers and women with anorexia needed to forge stronger alliances in order to reduce loss to follow-up.

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