Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review

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CRD summary
This review evaluated the effect of oral contraceptives on bone mineral density. The authors concluded that there is good evidence of a positive effect in perimenopausal women and fair evidence of a positive effect in hypothalamic oligo/amenorrhoeic premenopausal women. Poor reporting of review methods and reliance on a few small randomised controlled trials mean that these results should be interpreted with caution.

Authors' objectives
To determine the effect of oral contraceptives (OCs) and other forms of hormone replacement therapy (HRT) on bone mineral density (BMD) in four specified groups of premenopausal and perimenopausal women.

Searching
MEDLINE, the Cochrane Database of Systematic Reviews, ACP Journal Club, DARE, the Cochrane Controlled Trials Register, CINAHL and SPORTDiscus were searched from inception to March 2005; the search terms were reported. The search terms indicated that only English language studies were eligible. The references of relevant articles were also checked.

Study selection
Study designs of evaluations included in the review
Inclusion criteria for study design were not specified. Randomised controlled trials (RCTs), cross-sectional studies, case series and a case report study were included in the review. The duration of the included RCTs ranged from 9 months to 3 years.

Specific interventions included in the review
Studies that examined the effects of oestrogen and/or progesterone replacement therapy (i.e. OCs or HRT) were eligible for inclusion. The included studies used different types, doses and formulations of OC; most studies used ethinyl oestradiol (10 to 100 microg, where reported) in combination with different progestins or other hormones (details were reported). Control treatments, where these existed, included other OC regimens, progestins, calcium, placebo and no treatment.

Participants included in the review
Studies of healthy premenopausal, 'hypothalamic' oligo/amenorrhoeic premenopausal, anorexic premenopausal, or perimenopausal women were eligible for inclusion.

Outcomes assessed in the review
Studies that examined the effects on BMD were eligible for inclusion. The included studies measured BMD using dual-energy X-ray absorptiometry, dual-photon absorptiometry, single-photon absorptiometry and computed tomography. The review also assessed bone metabolism; this was measured in individual studies using N-telopeptides, deoxypyridinoline, bone-specific alkaline phosphatase, pyridinoline and creatinine.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the primary studies was evaluated using the Oxford Centre for Evidence-Based Medicine levels of
evidence, based on study design; criteria included sample size, randomisation, specific inclusion criteria, adequate follow-up and blinding. The levels of evidence ranged from 5 (expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles) to 1a (systematic review with homogeneity of RCTs).

The authors did not state how the quality assessment was performed.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The results from individual studies were classified as having a positive effect, no effect or a negative effect on the outcomes of interest. The results from controlled trials tended to be reported as changes from baseline in the review.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a narrative, grouped by population (healthy premenopausal, 'hypothalamic' oligo/amenorrhoeic premenopausal, anorexic premenopausal or perimenopausal) and outcome (measurement of BMD or biochemical measurement of bone metabolism).

How were differences between studies investigated?
Differences in study design were explored.

**Results of the review**
Seventy-five studies were reviewed: 11 RCTs (n=544), 28 cohort studies (n=3,256), 32 cross-sectional studies (n=19,547), 3 case series (n=94) and 1 case report.

BMD.

Healthy premenopausal women: 46 studies, including 4 RCTs (n=246), were reviewed. All 4 RCTs reported no effect on BMD for OCs compared with baseline controls. Three of the 16 cohort studies, 7 of the 25 cross-sectional studies, and the case series reported positive effects of OCs on BMD; other studies reported no effect or negative effects.

Oligo/amenorrhoeic premenopausal women: 10 studies, including 3 RCTs (n=122), were reviewed. Two of the RCTs reported a positive effect of OCs on BMD; one compared with placebo and one compared to baseline. The third RCT reported no increase in BMD from baseline with oestrogen treatment. Five of the 6 cohort studies reported positive effects of OCs on BMD, while the case series reported negative effects.

Anorexic premenopausal women: 8 studies, including 3 RCTs (n=159), were reviewed. All 3 RCTs reported no effect of OCs on BMD. The 2 cross-sectional studies reported positive effects of OCs on BMD; other studies (2 cohort studies and 1 case series) reported no effect or negative effects.

Perimenopausal women: 11 studies, including 1 RCT (n=17), were reviewed. The RCT reported a non significant increase in BMD in OC users compared to baseline. All 4 cohort studies and 3 of the 5 cross-sectional studies reported positive effects of OCs on BMD; other studies (2 cross-sectional studies and 1 case series) reported no effect.

Bone metabolism (RCTs only).

Healthy premenopausal women: 3 of the 4 RCTs reported a positive effect of OCs on bone metabolism.

Oligo/amenorrhoeic premenopausal women: 1 RCT (n=45) reported a positive effect of OCs on bone metabolism. Anorexic premenopausal women: 1 RCT reported a non significant decrease from baseline in urinary N-telopeptides with OCs.
Authors’ conclusions
There is good evidence for a positive effect of OCs on BMD in perimenopausal women, fair evidence of a positive effect in hypothalamic oligo/amenorrheic premenopausal women, and limited evidence of a positive effect in anorexic and healthy premenopausal women. Further RCTs should be carried out to confirm these results.

CRD commentary
The review question was supported by clear inclusion criteria in terms of the intervention, population and outcomes; inclusion criteria for study design were not specified. Several relevant electronic databases were searched, although the authors appeared to restrict their search by language. The methods used to select studies, assess quality and extract the data were not reported, thus it was not possible to assess the likelihood of bias or error being introduced at these stages. The authors stated that quality was assessed using specified criteria but the results of this assessment were not reported; this makes it impossible for readers to adequately assess the quality of the evidence. In the review, the results from individual studies were generally compared with baseline values rather than controls, which might have undermined the categorisation of the level of evidence for some of the included RCTs.

A narrative synthesis was appropriate given the heterogeneity between studies in terms of study design, intervention (type, dose and duration) and outcome measurement. It would have been useful to have had estimates of effect and confidence intervals from the RCTs if they were available, as the absence of this information limits the reader’s ability to determine the reliability of the results. Only positive results of OCs on bone metabolism were reported, and it was unclear whether any studies were identified that reported no effects or negative effects. Potential reasons for differing results among the studies were not explored. The review presented limited evidence from a small number of RCTs with appropriate control groups, so any conclusions cannot be considered definitive. This lack of RCTs and the small data sets of the RCTs found, in addition to the substantial clinical heterogeneity, support the authors’ comments that further research is required to substantiate these results.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further large, longitudinal RCTs are required to determine the duration of treatment and optimal formulations. Future RCTs should also account for skeletal maturity, as well as reproductive maturity, and trialists should use consistent definitions in women with menstrual dysfunction.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.