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

S L Liu, C M Lebrun

Seventy five articles on the effect of oral contraceptives and other hormone replacement on bone density in premenopausal and perimenopausal women were reviewed. The evidence was appraised using the Oxford Centre for Evidence-Based Medicine levels of evidence. There is good evidence for a positive effect of oral contraceptives on bone density in perimenopausal women, and fair evidence for a positive effect in “hypothalamic” oligo/amenorrheic premenopausal women. There is limited evidence for a positive effect in healthy and anorexic premenopausal women. In hypothalamic oligo/amenorrheic women, baseline bone density has been shown to be significantly lower than that in healthy controls, therefore the decision to treat is clinically more important. The ideal formulation(s) and duration of treatment remain to be determined by further longitudinal and prospective randomised controlled trials in larger subject populations.

According to Statistics Canada’s 1996–1997 National Health Population Survey, 18% of Canadian women aged 15–49 use oral contraceptives (OCs). In female athletes, OC use is at least as common as in the general population. The health benefits of OCs are contraceptive—for example, pregnancy prevention, reduced risk of ectopic pregnancy—and non-contraceptive—for example, cycle control, prevention of ovarian cancer, and reduction in dysmenorrhoea and acne. Whereas the pharmacological effects of both oestrogen and progesterone on bone metabolism are widely supported in the literature, the clinical effects of OC use on bone mineral density (BMD) remain unclear. Conflicting views may stem from the many confounding variables that affect BMD, including age, race, genetics, illness, smoking, weight, exercise, diet, and oestrogen status. The last four are especially relevant to the female athlete population, in light of the increasing prevalence of the female athlete triad. Compared with the general population, the higher levels of impact loading (in the setting of inadequate hormonal and nutritional status) may increase the female athlete’s risk of fractures and other skeletal injuries. Consequently, the female athlete faces unique concerns with respect to bone health; thus any effects of sustained OC use on BMD are of paramount importance. This review critically examines the literature to determine the effect of OCs and other forms of hormone therapy on BMD in four groups of women: healthy premenopausal, “hypothalamic” oligo/amenorrheic, anorexic premenopausal, and perimenopausal.

THE FEMALE ATHLETE TRIAD
First described in the early 1990s, the female athlete triad is a clinical syndrome comprising one or more of three specific components: disordered eating, amenorrhoea, and osteoporosis. The World Health Organization (WHO) classifies BMD by T score—that is, the number of standard deviations below peak BMD—as follows: $<-1$ is normal; $-1$ to $-2.5$ is osteopenia; $>-2.5$ is osteoporosis. However, the International Society for Clinical Densitometry claims that the WHO classification should not be applied to healthy premenopausal women because it is based on studies in postmenopausal women. Further, recent data suggest that the female athlete triad should use osteopenia as a defining criterion rather than osteoporosis, to more accurately reflect the greater prevalence of osteopenia in the female athlete population.

The female athlete triad is characterised by a negative energy balance, created when energy expenditure exceeds intake. This can be due to inadequate energy intake, excessive exercise, or a combination of both. A negative energy balance invariably leads to disruption of the hypothalamic-pituitary-ovarian axis, ovarian suppression, and various forms of menstrual dysfunction (including shortened luteal phase, oligomenorrhea, and amenorrhoea). Ultimately, hypothalamic-pituitary-ovarian axis, ovarian suppression, and various forms of menstrual dysfunction (including shortened luteal phase, oligomenorrhea, and amenorrhoea) cause the female athlete to experience decreased BMD. Management of the female athlete triad is multidisciplinary, involving doctors, psychologists, nutritionists, and nutritionists. However, the use of OCs to treat decreased BMD found in patients with the female athlete triad is controversial.

PHYSIOLOGICAL EFFECTS OF OESTROGEN AND EXERCISE ON BONE
Oestrogen plays a critical role in skeletal homoeostasis, with well recognised beneficial effects on bone. It is well known that exercise increases bone density, but the exact mechanism is not fully understood. The effect of exercise on bone density is complex and depends on a number of factors, including the type of exercise, the intensity of exercise, the duration of exercise, and the gender of the athlete. In female athletes, the effect of exercise on bone density is likely to be influenced by the presence of OCs, which can affect bone mineral density (BMD) in a number of ways. OCs have been shown to reduce bone turnover and increase BMD in healthy women, but their effect on bone density in female athletes is less clear. Moreover, the use of OCs may affect the efficacy of exercise in increasing bone density. The effect of exercise on bone density in female athletes is likely to be influenced by a combination of factors, including the type of exercise, the intensity of exercise, the duration of exercise, and the gender of the athlete. The effect of exercise on bone density in female athletes is likely to be influenced by a combination of factors, including the type of exercise, the intensity of exercise, the duration of exercise, and the gender of the athlete.
on bone mass, but the mechanisms by which it acts remain unclear. At the cellular level, oestrogen exerts effects on both osteoclast and osteoblast function, resulting in tonic inhibition of bone turnover and maintenance of the balance between bone resorption and formation.10 It is believed that oestrogen acts directly on bone cells in a receptor-mediated manner, as suggested by oestrogen receptor expression in both osteoblasts11 and osteoclasts.22 However, oestrogen also mediates indirect actions on bone through effects on hormones, such as calcitonin and parathyroid hormone, and on cytokines and growth factors.11

Exercise also has an important effect on BMD. It has been proposed that bone is capable of sensing biomechanical strain through an internal “mechanostat”, and adjusts the level of remodelling accordingly to increase bone accrual.13 This pathway is oestrogen dependent, as oestrogen deficiency alters the set point of the mechanostat, thereby impairing detection of biomechanical strain.10 The result is an inadequate level of bone remodelling and accretion. Chronically impaired response to strain and persistent inadequate bone remodelling and accretion potentially contribute to bone loss. Therefore, in physically active hypo-oestrogenic women—that is, women with the female athlete triad—OCs may be beneficial in “resetting” the mechanostat and restoring the appropriate homeostatic response of bone to exercise.

METHODS

Study selection

The electronic databases Medline, the Cochrane database of systematic reviews (CDSR), ACP journal club, database of abstracts of reviews of effects (DARE), Cochrane central register of controlled trials (CCTR), cumulative index to nursing and allied health literature (CINAHL), and SPORTDiscus were searched to identify potentially relevant articles up until March 2005. Searches used a combination of medical subject headings and keywords (table 1).

There were 327 hits from Medline, 212 from CINAHL, 30 from CDSR, ACP journal club, DARE, and CCTR (combined), and 17 from SPORTDiscus. Titles and abstracts were scanned to eliminate duplicates and to assess for relevance. Additional references were found through bibliographic searches of all retrieved articles.

Studies were included if they (a) examined effects on BMD, (b) included healthy, “hypothalamic” oligo/amenorrhoeic, or anorexic premenopausal or perimenopausal women, and (c) included oestrogen and/or progestosterone replacement therapy—that is, OCs or hormone replacement therapy—as a treatment.

Quality assessment and data extraction

The quality of evidence was appraised using the Oxford Centre for Evidence-Based Medicine levels of evidence,15 based on study design, including: sample size, randomisation, specific inclusion criteria, adequate follow up, and blinding (table 2).

Articles were classified into one of four groups according to study population (healthy premenopausal, “hypothalamic” oligo/amenorrhoeic premenopausal, anorexic premenopausal, perimenopausal), then subdivided by study design (randomised controlled trial (RCT), cohort, cross sectional, case series, case report) and by effect (positive, negative, no effect). Data summarised include OC exposure (formulation, dose) and outcome (measurement of BMD).

RESULTS

Study selection

Seventy five studies were reviewed16–90: 11 RCTs,26–29 62 63 69 74–76 78 80 82 84–89 three case series,54 78 90 and one case report71 (table 3). Tables 4–14 give descriptions of each study. The results focus on RCTs, as they provide the strongest evidence.

Data extraction

Healthy premenopausal women

Forty six studies in healthy premenopausal women were reviewed. Ten (three cohort,16–18 seven cross sectional19–25) showed a positive effect, 29 (four RCTs,26–29 nine cohort,30–38 15 cross sectional,39–53 one case series54) showed no effect, and seven (four cohort,55–58 three cross sectional59–61) showed a negative effect. All of the RCTs showed no effect on BMD, as measured by either dual energy x ray absorptiometry (DXA)26 27 29 or quantitative computed tomography.20 However, three of the four RCTs also showed a positive effect on bone turnover, as shown by decreased urinary concentrations of the bone resorption markers pyridinoline, deoxypyridinoline,27 29 and cross linked N-telopeptides.20 Further, the RCTs were comparison studies evaluating the effects of different doses/formulations of OCs, but two did not include a control group,26 28 and two used self selected

| Table 2 Oxford Centre for Evidence-based Medicine Levels of Evidence |
|--------------------------|----------------|----------------|----------------|----------------|----------------|
| Level | Evidence |
| 1a | Systematic review (with homogeneity) of RCTs |
| 1b | Individual RCT with narrow confidence interval |
| 1c | All or none |
| 2a | Systematic review (with homogeneity) of cohort studies |
| 2b | Individual cohort study (including low quality RCT; e.g. <80% follow up) |
| 2c | “Outcomes” research, ecological studies |
| 3a | Systematic review (with homogeneity) of case-control studies |
| 3b | Individual case-control study |
| 4 | Case series (and poor quality cohort and case-control studies) |
| 5 | Expert opinion without explicit critical appraisal, or based on physiology, bench research, or first principles |

RCT, Randomised controlled trial.
### Table 3 Summary of articles reviewed

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort (level 2b, level 4)</td>
<td>Becker et al</td>
<td>156 college age women</td>
<td>Current OC users (n = 34) v non-users (n = 33)</td>
<td>Forearm SPA, spine, total body DPA</td>
<td>Total body (but not forearm, spine) BMD positively correlated with OC use</td>
</tr>
<tr>
<td>Cross sectional</td>
<td>Goldsmith &amp; Johnston</td>
<td>2199 pre- and post-menopausal women (ages 15–79)</td>
<td>OC users (n = 100 µg mestranol, n = 332) v non-users (n = 1118)</td>
<td>Distal radius 125I photon absorptiometry</td>
<td>Significant correlation between duration of OC use and BMD (greatest in those with 10 years OC use)</td>
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<tr>
<td></td>
<td>Lindsay et al</td>
<td>57 women (ages 25–35)</td>
<td>Ever OC users (n = 30) v non-users (n = 24)</td>
<td>Lumbar spine DPA</td>
<td>Significant association between smoking and change in BMD in women older than 40 years of age</td>
</tr>
<tr>
<td></td>
<td>Kleerekoper et al</td>
<td>2297 women (24% pre-, 76% post-menopausal)</td>
<td>Ever OC users (n = 29.7% ever OC users) v non-users</td>
<td>Forearm SPA, lumbar spine DPA</td>
<td>Significant association between OC use and BMD (greatest in those with 10 years OC use)</td>
</tr>
<tr>
<td></td>
<td>Laitinen et al</td>
<td>293 Finnish women (186 pre-, 95 post-menopausal, 12 unknown, ages 20–76)</td>
<td>Premenopausal women v never users (n = 65)</td>
<td>Lumbar spine, proximal right femur DXA</td>
<td>Significant correlation between OC use and BMD in premenopausal women</td>
</tr>
<tr>
<td></td>
<td>Pasco et al</td>
<td>710 Australian women (511 pre-, 172 post-menopausal, 27 unknown, ages 20–69)</td>
<td>Ever OC users (n = 579) v never users (n = 131)</td>
<td>Lumbar spine, proximal femur, whole body, distal forearm DXA</td>
<td>Significant correlation between spiral BMD and cumulative OC exposure in white but not black women</td>
</tr>
<tr>
<td></td>
<td>Cobb et al</td>
<td>476 black &amp; white women (ages 18–30)</td>
<td>Lifetime history of OC use by questionnaire (quantitative measure)</td>
<td>Spine, whole body, hip DXA</td>
<td>Significant correlation between spiral BMD and cumulative OC exposure in white but not black women</td>
</tr>
<tr>
<td></td>
<td>Wallace &amp; Ballard</td>
<td>42 white women (ages 19–25)</td>
<td>Current OC users (n = 20) v non-users (n = 22)</td>
<td>Lumbar spine, total hip femoral neck, trochanter total body DPA</td>
<td>Significant correlation between spiral BMD and cumulative OC exposure in white but not black women</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; SPA, single photon absorptiometry; DPA, dual photon absorptiometry; EE, ethinyl oestradiol; DMPA, desogestrel; deoxypyrindoline; mestranol; EE did not, mestranol increase bone mineralisation (but OCs containing 100 µg mestranol increase bone mineralisation (but OCs containing 100–80 µg mestranol or 50–100 µg EE did not); smoking was associated with a larger negative change in BMD than in non-smokers; overall, OC use increased BMD (2.3% increase in BMD; desogestrel 0.3% increase in BMD).
<table>
<thead>
<tr>
<th>Study design</th>
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</thead>
<tbody>
<tr>
<td>RCT (level 1b, 20, 22, 25 level 2b)</td>
<td>Castelo-Branco et al</td>
<td>67 women (ages 19–29)</td>
<td>35 µg EE + 2 µg CA (n = 35) v 30 µg EE + 150 µg desogestrel (n = 32) for 24 months</td>
<td>DXA</td>
<td>No changes in BMD from baseline in either group</td>
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<tr>
<td></td>
<td>Nappi et al</td>
<td>60 women (ages 22–34)</td>
<td>20 µg EE + 75 µg gestodene (n = 20) v 15 µg EE + 60 µg gestodene (n = 20) v control (n = 20) for 12 months</td>
<td>Lumbar spine DXA; urinary PYY, D-PYR, serum osteocalcin</td>
<td>No changes in BMD from baseline in any group; decrease in PYY, D-PYR in OC treated groups suggesting decreased resorption</td>
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<tr>
<td></td>
<td>Endrikat et al</td>
<td>48 women (ages 20–38)</td>
<td>30 µg EE + 150 µg levonorgestrel (n = 25) v 20 µg EE +100 µg levonorgestrel (n = 23) for 36 months</td>
<td>Lumbar spine qCT; serum BSAP, urinary NTx</td>
<td>No changes in BMD from baseline in either group; decrease in NTx in both groups (suggesting decreased resorption)</td>
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<tr>
<td></td>
<td>Nappi et al</td>
<td>71 women (ages 22–34)</td>
<td>30 µg EE+3 mg drospirenone (n = 24) v 30 µg EE+75 µg gestodene (n = 24) v control (n = 23) for 12 months</td>
<td>Lumbar spine DXA; serum &amp; urinary Ca++, serum osteocalcin, urinary PYY, D-PYR</td>
<td>Decrease in PYY, D-PYR in both OC treated groups from baseline (suggesting decreased resorption); trend to increased BMD in never users in EE-drospirenone group</td>
</tr>
<tr>
<td>Cohort (level 2b)</td>
<td>Mazess &amp; Barden</td>
<td>300 women (ages 20–39)</td>
<td>50% past/current OC users, 50% never users</td>
<td>Lumbar spine DPA, radius SPA</td>
<td>No association between OC use and BMD</td>
</tr>
<tr>
<td></td>
<td>Cromer et al</td>
<td>48 women (ages 12–21)</td>
<td>30 µg EE + 150 µg desogestrel (n = 9) v Norplant (n = 7) v Depo-Provera (n = 15) v control (n = 17) for 12 months</td>
<td>Lumbar spine DXA</td>
<td>No significant difference between change in BMD in OC treated group (1.5% increase in BMD) v control (2.9% increase in BMD)</td>
</tr>
<tr>
<td></td>
<td>Lloyd et al</td>
<td>62 white women (followed from age 12–20 years)</td>
<td>OC users (‘low dose monophasic’) (n = 28) v non-users (n = 34)</td>
<td>Proximal femur DXA</td>
<td>No effect of OC treatment on peak bone mass or rate of acquisition</td>
</tr>
<tr>
<td>Cohort (level 4, 34 level 2b)</td>
<td>Reed et al</td>
<td>245 women (ages 18–39)</td>
<td>Current OC users (80%) on 30–35 µg EE (n = 86) v DMPA (n = 47) v control (n = 116)</td>
<td>Lumbar spine, proximal femur, total body DXA</td>
<td>No change in BMD from baseline in either group</td>
</tr>
<tr>
<td></td>
<td>Lara-Torre et al</td>
<td>148 women (ages 11–21)</td>
<td>New OC users (n = 71) v new DMPA users (n = 58) v control (n = 19) over 24 months</td>
<td>Lumbar spine DXA</td>
<td>No change in BMD from baseline in OC users</td>
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<tr>
<td></td>
<td>Lloyd et al</td>
<td>80 women (ages 12–22)</td>
<td>OC users (for &gt;=6 months, and still using at age 22) (n = 33) v non-users (n = 17)</td>
<td>Total body, bilateral proximal femur DXA</td>
<td>No difference in BMD between OC users and non-users</td>
</tr>
<tr>
<td></td>
<td>Berenson et al</td>
<td>191 women (ages 18–33)</td>
<td>OC (35 µg EE+1 mg norethindrone or 30 µg EE+0.15 mg desogestrel) (n = 86) v DMPA (n = 47) v control (n = 158) for 24 months</td>
<td>Lumbar spine DXA</td>
<td>No difference in BMD change from baseline between OC groups and control (decrease in BMD from baseline in DMPA group v control)</td>
</tr>
<tr>
<td></td>
<td>Paoli et al</td>
<td>54 women (ages 20–30)</td>
<td>30 µg EE+3 mg drospirenone (n = 28) v control (n = 26) for 6 months</td>
<td>Heel DXA-laser; serum osteocalcin, BSAP, urinary PYY, D-PYR</td>
<td>No change in BMD from baseline in any group; decrease in osteocalcin, BSAP, PYY in OC group (suggesting decreased bone turnover)</td>
</tr>
<tr>
<td></td>
<td>Rame et al</td>
<td>370 women (ages 12–18)</td>
<td>20 µg EE+100 µg levonorgestrel (n = 165) v DMPA (n = 53) v control (n = 152) for 12 months (n = 78) v non-users (n = 8)</td>
<td>Lumbar spine, hip DXA; serum BSAP, urinary D-PYR</td>
<td>Increase in BSAP in control v OC, but no difference in BMD between groups</td>
</tr>
<tr>
<td>Cross sectional</td>
<td>Sowers et al</td>
<td>86 women (ages 20–35)</td>
<td>OC users (for &gt;2 years) (n = 78) v non-users (n = 8)</td>
<td>Bone mass by 125I photon absorptiometry</td>
<td>No difference in bone mass between ever v never users or between current v past users</td>
</tr>
<tr>
<td></td>
<td>Hreschynshyn et al</td>
<td>352 women (pre- and post-menopausal, ages 24–79)</td>
<td>Ever OC users (n = 116) v never users (n = 236)</td>
<td>Lumbar spine, femoral neck DPA</td>
<td>No difference in BMD between ever OC users and never users</td>
</tr>
<tr>
<td></td>
<td>Lloyd et al</td>
<td>25 women</td>
<td>OC users (minimum 50 µg mestranol/day) (n = 14) v non-users (n = 11)</td>
<td>Lumbar spine qCT</td>
<td>No difference in BMD between OC users and non-users</td>
</tr>
<tr>
<td></td>
<td>Stevenson et al</td>
<td>284 white women (112 pre-, 172 post-menopausal)</td>
<td>OC users v non-users</td>
<td>Lumbar spine, proximal femur DPA</td>
<td>No association between OC use and BMD in premenopausal women</td>
</tr>
<tr>
<td></td>
<td>Hall et al</td>
<td>165 women (pre- and post-menopausal, ages 4–80)</td>
<td>Ever OC users (n = 69) v never users (n = 96)</td>
<td>Lumbar spine DXA</td>
<td>No difference in BMD between ever OC users and non-users in any age group</td>
</tr>
<tr>
<td></td>
<td>Murphy et al</td>
<td>841 women (229 pre-, perimenopausal, 583 postmenopausal, 29 unknown)</td>
<td>Ever OC users (n = 159 pre-, perimenopausal; n = 182 postmenopausal; n = 11 unknown) v never users (n = 70 pre-, peri-menopausal; n = 40) postmenopausal; n = 18 unknown)</td>
<td>Lumbar spine, hip DXA</td>
<td>No difference in BMD between ever OC users and non-users</td>
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</table>
control groups choosing not to receive contraception,\(^\text{27-29}\) which may have affected the validity of the results. No RCT showed a negative effect. But notably, two cohort studies\(^\text{48,56}\) and one cross sectional study\(^\text{47}\) examined the combination of exercise and OCs on BMD. As previously discussed, exercise is believed to have a positive effect on BMD, according to Frost’s mechanostat theory.\(^\text{14}\) However, Burr et al\(^\text{48}\) showed that either exercise or OCs alone was associated with a suppression of the normal increase in femoral neck BMD in women 18–31 years old, but the combination of exercise and OCs together had a less suppressive effect than either alone.

Table 5 (Continued.)

<table>
<thead>
<tr>
<th>Study design</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Petitti et al(^\text{47})</td>
<td>2474 women (ages 30–34)</td>
<td>Ever OC users vs never users</td>
<td>Lumbar spine, total body, total hip, distal radius DXA, serum osteocalcin, BSAP, C terminal propeptide of type I collagen, urinary NTx and PYR</td>
<td>No difference in BMD between ever OC users and never users</td>
<td></td>
</tr>
<tr>
<td>Ott et al(^\text{48})</td>
<td>227 women (ages 18–39)</td>
<td>OC users (for ≥2 years, n = 63) vs DMPA users (for ≥2 years, n = 63) vs control (no hormonal contraception, n = 63)</td>
<td>Lumbar spine, total body, total hip, distal radius DXA, serum C-telopeptides, PTH, osteocalcin, urinary NTx</td>
<td>No difference in BMD between any of the groups; decrease in osteocalcin and NTx in OC users vs non-users (suggesting decreased bone turnover)</td>
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</tr>
<tr>
<td>Perotti et al(^\text{49})</td>
<td>189 women (ages 30–34)</td>
<td>Non-dominant radius SXA</td>
<td>No difference in BMD between any of the groups</td>
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<tr>
<td>Hawker et al(^\text{50})</td>
<td>830 women (ages 19–35)</td>
<td>Current OC users (n = 223) vs past OC users (n = 512) vs never users (n = 95)</td>
<td>Lumbar spine, femoral neck, Ward’s triangle, greater trochanter, radius, ulna DPA, Whole body DXA</td>
<td>No association between OC use and BMD</td>
<td></td>
</tr>
<tr>
<td>Wanicchoetokul et al(^\text{51})</td>
<td>155 women (ages 30–34)</td>
<td>OC users (n = 59) vs DMPA users (n = 34) vs control (n = 62)</td>
<td>Lumbar spine, femoral neck, greater trochanter, radius, ulna DPA, Whole body DXA</td>
<td>No difference in BMD between OC users and control</td>
<td></td>
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<tr>
<td>Afghani et al(^\text{52})</td>
<td>39 Hispanic pre/perimenopausal women (ages 22–51)</td>
<td>Current OC user vs non-user</td>
<td>No relation between current OC use and BMD (but no information about duration of use, past use, dose, etc)</td>
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<tr>
<td>Meyer et al(^\text{53})</td>
<td>61 women (40 athletes, 19 eumenorrhoeic, 21 oligoamenorrhoeic)</td>
<td>Current OC user vs non-user</td>
<td>Areal BMD of whole body, lumbar spine, proximal femur, femoral neck, greater trochanter, radius, ulna DPA, Whole body DXA</td>
<td>No association between OC use and areal BMD in athlete group</td>
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<tr>
<td>Case series (level 4)</td>
<td></td>
<td></td>
<td>Distal radius DPA; serum BSAP, urinary hydroxyproline/Cr</td>
<td>NS increase in BMD; decrease in BSAP, hydroxyproline (suggesting decreased bone turnover)</td>
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</table>

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; EE, ethinyl oestradiol; CA, cyproterone acetate; DXA, dual energy x ray absorptiometry; PPR, pyridinoline; D-PPR, deoxypyridinoline; qCT, quantitative computed tomography; BSAP, bone specific alkaline phosphatase; NTx, N-telopeptides; DPA, dual photon absorptiometry; SPA, single photon absorptiometry; DMPA, desoxymedroxyprogesterone acetate; SXA, single energy photon absorptiometry; PTH, parathyroid hormone; Cr, creatinine; NS, non-significant.

Oligo/amenorrheic premenopausal women

Ten studies on oligo/amenorrheic premenopausal women were reviewed. Menstrual irregularities were classified as “hypothalamic” oligo/amenorrhea—that is, functional menstrual irregularity—or that occurring in the absence of an organic cause (except for two cohort studies which included subjects with primary ovarian failure,\(^\text{44}\)) and from a variety of unspecified causes.\(^\text{45}\) Although these conditions often occur in athletic females, as previously discussed, it is the energy
deficit, rather than the activity itself, that leads to the menstrual dysfunction. In the reproductive literature, eumenorrhoea is defined as cycles with intervals of 25–34 days, whereas oligomenorrhoea typically refers to menstrual cycles longer than 35 days. The term amenorrhoea (secondary amenorrhoea) connotes a persistent absence of menstrual cycles, commonly for three or more months after the establishment of regular menses. However, confusion often arises when comparing studies, because of the inconsistency of definitions, particularly in earlier research.

Of the 10 studies of OC and other hormone replacement in this population, seven (two RCTs, five cohort studies) showed a positive effect, two (one RCT, one cohort) showed no effect, and one case report showed a negative effect on BMD. In all studies that compared baseline BMDs with that of healthy controls or age matched reference values, baseline BMDs were significantly lower in the oligo/amenorrhoeic group.65–71 Hergenroeder et al reported that the effects of OCs, compared with medroxyprogesterone or placebo. Although well designed, this was a small study with only five subjects per treatment group, followed over a 12 month time span. In a somewhat larger study (18–24 subjects per group), Castelo-Branco et al examined the effects of two doses (20 or 30 μg) of ethinyl oestradiol-containing OCs on lumbar spine BMD. Both doses increased BMD, whereas the BMD of the control group decreased.66 Conversely, Gibson et al showed that lumbar spine and hip BMD did not significantly change with OCs, calcium carbonate, or control. This trial was conducted over 18 months; however, data from only nine months were reported because of a high dropout rate. Further, the OC treated group in this study did show a non-significant increase in BMD after nine months. No RCT showed a negative effect of OC treatment on BMD.

### Table 6 Healthy premenopausal women: negative effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort (level 2b, level 4)</td>
<td>Polati et al&lt;sup&gt;65&lt;/sup&gt;</td>
<td>200 women (ages 19–22)</td>
<td>20 μg EE+0.15 mg desogestrel (n = 100) v control (n = 100) for 60 months</td>
<td>Lumbar spine DXA; serum BSAP, urinary hydroxyproline Cr</td>
<td>No change in BMD in treated group, v increase in BMD in control group; no change in BSAP or hydroxyproline levels in either group</td>
</tr>
<tr>
<td></td>
<td>Burr et al&lt;sup&gt;64&lt;/sup&gt;</td>
<td>46 women (ages 18–31)</td>
<td>Non-exercisers/ non-OC users (n = 10) v non-exercisers + &lt; 50 μg EE (n = 13) v exercisers/ non-OC users (n = 8) v exercisers + &lt; 50 μg EE (n = 15)</td>
<td>Femoral neck DXA; serum osteocalcin, BSAP, acid phosphatase, urinary hydroxyproline Cr</td>
<td>Either OC use or exercise alone is associated with suppression of the normal increase in femoral neck bone mass/mechanical strength; combination of OC use and exercise has less suppressive effect than either alone</td>
</tr>
<tr>
<td>Cross sectional</td>
<td>Weaver et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>179 women (ages 18–31)</td>
<td>Non-exercisers/ non-OC users (n = 40) v non-exercisers + &lt; 50 μg EE (n = 37) v exercisers/ non-OC users (n = 27) v exercisers + &lt; 50 μg EE (n = 40)</td>
<td>Lumbar spine, total body total hip DXA; radius SPA; serum osteocalcin, BSAP, acid phosphatase, urinary hydroxyproline Cr</td>
<td>Significant interaction between OC use and exercise, such that a combination of OC use and exercise compromises attainment of peak spinal BMD</td>
</tr>
<tr>
<td></td>
<td>Cramer et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>215 women (ages 12–18)</td>
<td>20 μg EE+100 μg levonorgestrel (n = 79) v DMPA (n = 29) v control (n = 107) over 12 months</td>
<td>Lumbar spine, total hip, femoral neck, Ward’s triangle, trochanter DXA</td>
<td>Increase in spine and hip BMD in both OC and control groups, but increase in OC group was significantly less than that in control group</td>
</tr>
<tr>
<td></td>
<td>Cross sectional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hartard et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>128 women (ages 20–35)</td>
<td>Long term exercise/short term use (n = 30) v long term exercise/long term OC use (n = 37) v short term exercise/long term OC use (n = 31) v short term exercise/ short term OC use (n = 30)</td>
<td>Lumbar spine, femoral neck DXA</td>
<td>Highest BMD in long term exercise/ short term OC use group; no differences in mean BMD between short term exercise/long term OC use and short term exercise/short term OC use; overall, OC use counteracts beneficial effect of exercise on BMD</td>
</tr>
<tr>
<td></td>
<td>Prior et al&lt;sup&gt;70&lt;/sup&gt;</td>
<td>524 women (ages 25–45)</td>
<td>Ever OC users (for &gt;3 months) (n = 454) v never users (to &lt;3 months) (n = 70)</td>
<td>Lumbar spine, proximal femur DXA</td>
<td>Decrease in lumbar spine, trochanter BMD in ever OC users v never users</td>
</tr>
<tr>
<td></td>
<td>Hartard et al&lt;sup&gt;71&lt;/sup&gt;</td>
<td>69 female endurance athletes (ages 18–35)</td>
<td>OC group (use for &gt;3 years in women &lt;22 years old or use for &gt;50% of time after menarche in women age 22–35) (n = 31) v control (n = 38)</td>
<td>Lumbar spine, hip DXA</td>
<td>OC users had 7.9% lower lumbar spine and 8.8% lower proximal femur BMD than control</td>
</tr>
</tbody>
</table>

OC: Oral contraceptive; BMD, bone mineral density; EE, ethinyl oestradiol; DXA, dual energy x ray absorptiometry; BSAP, bone specific alkaline phosphatase; Cr, creatinine; SPA, single photon absorptiometry; DMPA, deoxymedroxyprogesterone acetate.

### Anorexic premenopausal women

Eight studies on premenopausal women with anorexia nervosa were reviewed. Subjects were defined as having anorexia nervosa by either the Diagnostic and statistical manual of mental disorders (DSM)-III or DSM-IV criteria (except for two studies, in which the criteria used were not explicitly stated). Two cross sectional studies showed a positive effect, five studies (three RCTs, one cohort, one case series) showed no effect, and one cohort study showed a negative effect. Klibanski et al found no overall change in lumbar spine BMD from baseline in either the oestrogen treated or control group. However, the effect of oestrogen on BMD was greatest in patients with the lowest initial body weight, and diminished with increasing patient weight. Control patients with a baseline body weight <70% of ideal experienced a significant decrease in BMD, whereas oestrogen treated patients with baseline body weight <70% of ideal did not experience any significant change in BMD, suggesting that, in anorexic women, oestrogen may have a body weight dependent effect on BMD. Gordon et al showed no effect of either dehydroepiandrosterone or OCs on total hip BMD in anorexic women. In both groups, non-significant increases in lumbar BMD and significantly decreased N-telopeptide concentrations were reported. Grinspoon et al examined the effect of OCs, recombinant human insulin-like
Table 7 Oligo/amenorrhoeic premenopausal women: positive effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (level 1b)</td>
<td>Hergenroeder et al**</td>
<td>24 women</td>
<td>35 µg EE+0.5–1 mg norethindrone (n = 5) v 10 mg medroxyprogesterone (n = 5) v placebo (n = 5) for 12 months</td>
<td>Lumbar spine, total body, femoral neck DXA</td>
<td>Increase in lumbar spine &amp; total body BMD in OC treated group v placebo; no change in BMD at any site in medroxyprogesterone treated group</td>
</tr>
<tr>
<td></td>
<td>Castelo-Branco et al**</td>
<td>64 women</td>
<td>30 µg EE+0.15 mg desogestrel (n = 24) v 20 µg EE+0.15 mg desogestrel (n = 22) v control (n = 18) for 12 months</td>
<td>Lumbar spine DXA</td>
<td>Increase in lumbar spine BMD in both OC treated groups; decrease in BMD in control group</td>
</tr>
<tr>
<td>Cohort (level 2b)</td>
<td>De Creë et al*</td>
<td>11 sportswomen with athletic menstrual irregularity (ages 18–29)</td>
<td>50 µg EE+2 mg cyproterone acetate (n = 7) v control (n = 4) for 8 months</td>
<td>Lumbar spine DPA, radius SPA</td>
<td>9.5% increase in lumbar spine BMD in OC treated group</td>
</tr>
</tbody>
</table>

Gulekli et al

Rickenlund et al

Haenggi et al

Cumming

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; EE, ethinyl oestriol; DXA, dual energy x ray absorptiometry; DPA, dual photon absorptiometry; SPA, single photon absorptiometry; NS, non-significant.

Table 8 Oligo/amenorrhoeic premenopausal women: no effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (level 2b)</td>
<td>Gibson**</td>
<td>34 women with athletic oligo/amenorrhoea</td>
<td>Oestrogen treated (1 mg oestriol+2 mg oestriol, days 1–12; 1 mg oestriol+2 mg oestriol+1 mg norethisterone acetate, days 13–22; 0.5 mg oestriol+1 mg oestriol, days 23–28)=1000 mg calcium carbonate (n = 10) v 1000 mg calcium carbonate (n = 14) v control (n = 10) for 18 months</td>
<td>Lumbar spine, Ward’s triangle, femoral neck, trochanteric region DXA</td>
<td>NS increase in BMD from baseline in oestrogen treated group</td>
</tr>
<tr>
<td>Cohort (level 2b)</td>
<td>Gremian et al**</td>
<td>30 female long distance runners (ages 19–37)</td>
<td>Each group received 30 µg EE+130 µg levonorgestrel for 10 months</td>
<td>Lumbar spine, total body DXA before and after 10 months of OC use</td>
<td>No change in BMD from baseline at any site in OC treated group; decrease in lateral lumbar spine BMD from baseline in oligo/amenorrhoeic group; lower osteocalcin levels in OC treated group than in other 2 groups</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; EE, ethinyl oestriol; DXA, dual energy x ray absorptiometry; NS, non-significant.
### Table 9  Oligo/amenorrhoeic premenopausal women: negative effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report</td>
<td>Zanker et al&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1 amenorrhoeic athlete (followed between age 24.8 to 36.9 years)</td>
<td>For the first 5 years, used 30 μg EE+150 μg desogestrel</td>
<td>Lumbar spine, proximal femur DXA</td>
<td>9.8% decrease in lumbar spine BMD and 12.1% decrease in proximal femur BMD during 5 years of OC use</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; EE, ethinyl oestradiol; DXA, dual energy x ray absorptiometry.

### Table 10  Anorexic premenopausal women: positive effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross sectional</td>
<td>Seeman et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>117 women (65 with AN; 12 with 1° amenorrhoea, 16 with 2° amenorrhoea taking OCs, 37 with 2° amenorrhoea not taking OCs; 52 healthy controls)</td>
<td>OC users v non-users</td>
<td>Lumbar spine, total body, proximal femur DXA</td>
<td>Higher BMD in healthy control women than in women with AN; greater mean lumbar spine BMD in women with AN taking OCs than in women with AN not taking OCs</td>
</tr>
<tr>
<td>Karlsson et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>366 women (77 non-OC users with AN, 58 OC users with AN, 26 women recovered from AN; 205 healthy controls)</td>
<td>OC users v non-users</td>
<td>Areal BMD by DXA, volumetric BMD calculated</td>
<td>Higher BMD in healthy control women than in women with AN; greatest reduction in BMD was in non-OC users with AN; lesser reduction in OC users with AN; least reduction in women recovered from AN</td>
<td></td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; AN, anorexia nervosa; DXA, dual energy x ray absorptiometry.

### Table 11  Anorexic premenopausal women: no effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (level 1b)</td>
<td>Klisbinski et al&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48 women with AN (ages 16-42)</td>
<td>0.625 mg Premarin/5 mg Provera (n=16) v 35 μg EE (n=6) v control (n=26) for 18 months</td>
<td>Lumbar spine CT</td>
<td>No significant changes in BMD between oestrogen treated and control groups; 4% increase in BMD in oestrogen treated patients with initial ideal body weight of &lt;70%; v 20% decrease in BMD in control patients with initial ideal body weight of &lt;70%</td>
</tr>
<tr>
<td>Gordon et al&lt;sup&gt;5&lt;/sup&gt;</td>
<td>51 women with AN (ages 14-28)</td>
<td>20 μg EE +0.1 mg levonorgestrel v 50 mg dehydroepiandrosterone for 12 months</td>
<td>Lumbar spine, total body, total hip, femoral neck, trochanter DXA; serum osteocalcin, BSAP, urinary NTx</td>
<td>NS increase in lumbar BMD in both groups; decrease in urinary NTx in both groups (suggesting decrease in resorption)</td>
<td></td>
</tr>
<tr>
<td>Grinspoon et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>60 women with AN</td>
<td>35 μg EE+0.4 mg norethindrone (n=15) v 30 μg/kg rhIGF-I (n=14) v 30 μg/kg rhIGF-I+35 μg EE+0.4 mg norethindrone (n=16) v control (placebo rhIGF-I, n OC) (n=15) for 9 months</td>
<td>Lumbar spine, total body, distal radius, total hip, femoral neck DXA</td>
<td>Factorial analysis: no effect of OC on BMD at any site; 4-group analysis: increase in AP lumbar BMD in combined rhIGF-I+OC group v baseline and v placebo; Overall: OCs may augment effects of rhIGF-I on BMD, but are not effective alone</td>
<td></td>
</tr>
<tr>
<td>Cohort (level 2b)</td>
<td>Golden et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>50 women with AN (ages 13-21)</td>
<td>Oestrogen treatment: OrthoTri-Cyclen (35 μg EE+0.18 mg norgestimate, days 1-7; 35 μg EE+0.215 mg norgestimate, days 8-14; 35 μg EE+0.25 mg norgestimate, days 15-21) (n=10), Ortho-Cyclen (35 μg EE+0.25 mg norgestimate) (n=6), Lo-Ovral (30 μg EE + 0.3 mg norgestimate) (n=2), Lo-Estrin (30 μg EE + 1.5 mg norethindrone) (n=2), Levolen (30 μg EE + 0.15 mg levonorgestrel) (n=1), Alesse (20 μg EE + 0.1 mg levonorgestrel) (n=1) v control (n=28) for 36 months</td>
<td>Lumbar spine, left hip DXA</td>
<td>Initial BMDs were decreased compared with the young adult reference mean; no significant changes in BMD from baseline in either oestrogen treated or control groups</td>
</tr>
<tr>
<td>Case series (level 4)</td>
<td>Mutiaz et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>38 women with AN (mean age 17.3 years)</td>
<td>50 μg EE-0.5 mg norgestrel for 12 months</td>
<td>Lumbar spine DXA</td>
<td>No change in BMD from baseline</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; AN, anorexia nervosa; EE, ethinyl oestradiol; CT, computed tomography; NS, non-significant; DXA, dual energy x ray absorptiometry; BSAP, bone specific alkaline phosphatase; NTx, N-telopeptides; rhIGF-I, recombinant human insulin-like growth factor I.
Oral contraceptives/hormone replacement and bone mineral density

**Table 12** Anorexic premenopausal women: negative effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort (level 2b)</td>
<td>Kreipe et al</td>
<td>4 women with AN (ages 17–28)</td>
<td>Oestrogen + progestin replacement (n = 2) v control (n = 2) for 6 months</td>
<td>Lumbar spine DXA</td>
<td>1.9% decrease in BMD in oestrogen-progestin treated group v 1.3% increase in BMD in control group</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; AN, anorexia nervosa; DXA, dual energy x ray absorptiometry.

**Table 13** Perimenopausal women: positive effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT (level 1b)</td>
<td>Volpe et al</td>
<td>17 perimenopausal women (ages 46–53)</td>
<td>OC treated (n = 8) v control (n = 9) for 36 months</td>
<td>Spine DXA</td>
<td>NS increase in BMD in OC users, decrease in BMD in non-users</td>
</tr>
<tr>
<td>Cohort (level 2b, 4)</td>
<td>Shargil et al</td>
<td>200 women (ages 41–49)</td>
<td>Triphasic OC (30 µg EE+0.05 mg levonorgestrel x6, 40 µg EE+0.075 mg levonorgestrel x5, 30 µg EE+0.125 mg levonorgestrel x10) (n = 100) v control (n = 100) for 36 months</td>
<td>Lumbar spine, hand bone mass x ray/CT</td>
<td>No change in OC users v 6% decrease in BMD in controls</td>
</tr>
<tr>
<td>Gambacciani et al</td>
<td>(level 3b)</td>
<td>32 perimenopausal women (ages 46–53)</td>
<td>30 µg EE+75 µg gestodene (n = 16) v 500 mg Ca²⁺ (n = 16) for 24 months</td>
<td>Radius DPA</td>
<td>Increase BMD with OC use</td>
</tr>
<tr>
<td>Gambacciani et al</td>
<td>(level 3b)</td>
<td>90 perimenopausal women (27 eumenorrhoeic, 54 oligomenorrhoeic)</td>
<td>20 µg EE+0.15 mg desogestrel (n = 27) v 500 mg Ca²⁺ (n = 27) for 24 months</td>
<td>Lumbar spine DXA</td>
<td>Increase in BMD with OC use v decrease in BMD with calcium</td>
</tr>
<tr>
<td>Gambacciani et al</td>
<td>(level 3b)</td>
<td>55 perimenopausal women (18 eumenorrhoeic, 37 oligomenorrhoeic)</td>
<td>20 µg EE+0.15 mg desogestrel v 500 mg Ca²⁺ for 24 months</td>
<td>Femoral neck, Ward’s triangle, trochanter DXA</td>
<td>Increase in femoral neck BMD from baseline v OC use v decrease in femoral neck, Ward’s triangle, trochanter BMD from baseline with calcium</td>
</tr>
<tr>
<td>Cross sectional</td>
<td>Erzelsberger et al</td>
<td>200 women (ages 46–53)</td>
<td>&gt;10 years OC use (n = 30) v never use (n = 120) for &gt;10 years</td>
<td>Forearm SPA</td>
<td>OC use for &gt;10 years associated with increase in BMD</td>
</tr>
<tr>
<td>Tuppurainen et al</td>
<td>(level 3b)</td>
<td>3222 women (98 peri-, 1940 post-menopausal)</td>
<td>29% ever OC use</td>
<td>Lumbar spine, femoral neck DXA</td>
<td>Ever OC users had increase spinal BMD v never users</td>
</tr>
<tr>
<td>Masaryk et al</td>
<td>(level 3b)</td>
<td>2038 women</td>
<td>18.3% ever OC use</td>
<td>Lumbar spine, hip DXA</td>
<td>Ever OC users had increase in spinal BMD v never users</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; DXA, dual energy x ray absorptiometry; NS, non-significant; EE, ethinyl oestradiol; CT, computed tomography; DPA, dual photon absorptiometry; SPA, single photon absorptiometry.

**Table 14** Perimenopausal women studies: no effect of oral contraceptives on bone mineral density

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of BMD/ bone metabolism</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross sectional</td>
<td>Fortney et al</td>
<td>352 women (ages 40–54)</td>
<td>Ever OC users (n = 260) v never users (n = 92)</td>
<td>Lumbar spine, radius DPA</td>
<td>NS increase in spinal BMD in OC users of longer duration and more recent use</td>
</tr>
<tr>
<td>Beksinska et al</td>
<td>(level 3b)</td>
<td>496 women (ages 40–49)</td>
<td>OC users (30–40 µg EE) (n = 106) v DMPA (n = 127)</td>
<td>Distal radius, midshaft ulna DXA</td>
<td>No significant difference in BMD between any of the groups</td>
</tr>
<tr>
<td>Case series</td>
<td>Volpe et al</td>
<td>37 women (ages 45–48)</td>
<td>20 µg EE+150 µg desogestrel for 24 months</td>
<td>Lumbar spine DPA</td>
<td>NS increase in BMD (increase 8%)</td>
</tr>
</tbody>
</table>

OC, Oral contraceptive; BMD, bone mineral density; DPA, dual photon absorptiometry; NS, non-significant; EE, ethinyl oestradiol; DMPA, desoxymedroxyprogesterone acetate; NET-EN, norethisterone enanthate; DXA, dual energy x ray absorptiometry.
growth factor I (IGF-I), OCs plus IGF-I, or placebo plus IGF-I on BMD at several skeletal sites. No effect of OCs on BMD was detected at any site by factorial analysis, but by four group analysis it was found that, despite being ineffective alone, OCs may augment the effects of IGF-I on BMD in anorexic women.76 No RCT showed a negative effect of OC treatment on BMD.

### Perimenopausal women
Eleven studies on perimenopausal women were reviewed. Eight (one RCT,80 four cohort,81–84 three cross sectional85–87) supported a positive effect, whereas three (two cross sectional,88 89 one case series90) showed no effect. Volpe et al91 showed a non-significant increase in spinal BMD in the OC treated group compared with a significant decrease in BMD in the control group. No study showed a negative effect of OC treatment on BMD.

### DISCUSSION
This review critically examines current literature to determine the effect of OCs (and other hormone treatment) on BMD in four groups: healthy premenopausal, “hypothalamic” oligo/amenorrheic premenopausal, anorexic premenopausal, and perimenopausal women. Because of the number and diversity of the studies, it was not possible to perform a formal meta-analysis of the results. However, the type of evidence, based on study type and including subject numbers, is summarised below.

There is good evidence supporting a positive effect of OCs on BMD in perimenopausal women. Of 11 studies found, eight (with a combined total of 5854 subjects) showed a positive effect, including one RCT (with 17 subjects). Three studies (of 885 women) did not find any effect. No study showed a negative effect.

There is also fair evidence supporting a positive effect of OCs on BMD in oligo/amenorrheic premenopausal women. Of 10 studies, seven (with a total of 379 subjects) showed a positive effect, including two RCTs in a total of 88 women. Although another RCT of 34 women reported no effect, there was still a non-significant trend towards increased BMD in the OC group in this study. In addition, a RCT of 45 women examining the effect of OCs on bone metabolism showed decreased markers of bone resorption in the OC treated group, compared with placebo, supporting a beneficial effect of OCs in this group94 (table 15). Only one case report showed a negative effect.

There is limited evidence supporting a positive effect of OCs on BMD in anorexic premenopausal women. Of eight studies, two cross sectional ones of 483 women found a positive effect. Five studies (with 247 total subjects) showed no effect. However, it appears that body weight at initiation of OC treatment may play a role in determining the effect of OCs on BMD.74 Thus, calculation of body weight, as a percentage of ideal, may be an important step in deciding whether to treat anorexic patients with OCs. This evidence may not be helpful in deciding treatment for women with the female athlete triad though, as anorexics are quite distinct in their hormonal condition and state of activity. Sundgot-Borgen & Torstveit92 reported that a higher percentage of Norwegian elite athletes met the criteria for subclinical eating disorders—that is, athletic amenorrhoea or “eating disorders not otherwise specified”—than for clinical eating disorders (anorexia or bulimia nervosa). Women with clinical eating disorders are more sedentary than women with the female athlete triad syndrome, and oestrogen deficiency appears to play less of a role, and IGF-I deficiency more of a role, in decreased BMD in women with clinical eating disorders than in those with the syndrome.76

There is limited evidence supporting a positive effect of OCs on BMD in healthy premenopausal women. Of 46 studies, 29 showed no effect, including all of the RCTs. However, one RCT95 showed a non-significant trend towards increased BMD, and three RCTs25–27 showed decreased concentrations of bone resorption markers in the OC group. Likewise, one RCT96 and two cohort studies97 98 examining the effect of OCs on bone metabolism also suggested similar beneficial results (table 15). A total of seven studies (cohort and cross sectional) of 1361 women suggested a negative effect of OCs on BMD. This is somewhat worrisome, and a variety of potential explanations were given.

Interestingly, there are also data from three studies showing that a combination of exercise and OC use in healthy premenopausal women may have a negative effect on BMD. Postulated reasons for the negative interaction between exercise and OC use are: inadequate bone mineralisation because of nutritional calcium deficiency,66 suppression of endogenous pituitary releasing hormone, oestrogen, and progesterone peaks with resultant alteration

### Table 15  Biochemical evidence: positive effect of oral contraceptives on bone metabolism

<table>
<thead>
<tr>
<th>Study design</th>
<th>Reference</th>
<th>No of patients</th>
<th>OC exposure</th>
<th>Measurement of bone metabolism</th>
<th>Results</th>
</tr>
</thead>
</table>
| Oligo/amenorrheic  
RCT (level 1b) | Grinspoon et al75 | 45 women with hypothalamic amenorrhea (ages 18–40) | OC group (35 μg EE–0.18 mg norgestimate, days 1–7, 35 μg EE–0.215 mg norgestimate, days 8–14; 35 μg EE–0.25 mg norgestimate, days 15–21) (n = 25) vs placebo (n = 20) for 3 months | NTx, D-PYR | Decrease in NTx and D-PYR in OC treated group (therefore decreased resorption) |
| Healthy premenopausal  
RCT (level 1b) | Pinter et al76 | 41 women (ages 20–27) | 30 μg EE–150 μg levonorgestrel (n = 21) vs control (n = 20) for 3 months | Serum BSAP and osteocalcin, urinary D-PYR | OC treated: BB genotype, decrease in osteocalcin; in BB genotype, decrease in BSAP and osteocalcin; lab genotype, no change. Control: no changes in any genotype. Decrease in PYR, D-PYR in OC-treated groups (suggesting decreased resorption) |
| Cohort (level 2b) | Paoletti et al77 | 30 women (ages 23–30) | 20 μg EE–75 μg gestodene (n = 10) vs 30 μg EE–75 μg gestodene (n = 10) vs control (n = 10) for 12 months | Urinary PYR, D-PYR | |
| Kiti et al78 | 30 women (mean age 23.7 years) | OC users v non-users | Urinary Ca²⁺/Cr ratio | Decrease in Ca²⁺/Cr with OC use (suggesting decreased resorption); effect more pronounced in non-smokers |

OC, Oral contraceptive; RCT, randomised controlled trial; EE, ethinyl oestradiol; NTx, N-telopeptides; D-PYR, deoxypyridinoline; BSAP, bone specific alkaline phosphatase; PYR, pyridinoline; Cr, creatinine.
of the bone mechanostat,95 and the differential effects of different progestins on BMD.99

According to the Oxford Centre for Evidence-Based Medicine levels of evidence,13 the strongest level of evidence (1a) is derived from a systematic review with homogeneity of RCTs. The next best level (1b) is from individual RCTs, with evidence from other study designs carrying less weight. In this review, focus was placed on the RCTs, with supporting evidence from other study types. All of the RCTs included had methodological limitations. In three of the RCTs, subjects were asked whether they desired contraception or not. Those that desired contraception were randomised to one of several treatment groups, and those who did not choose contraception served as the controls, necessitating the concern of self selection bias.27 28 63 Three other studies compared the effect of different types/doses of OCs on BMD, but did not include a non-treatment control group for comparison.26 28 75

Five studies had non-treatment control groups,26 62 77 78 80 but only one was placebo controlled.62 Only one study was double blinded,24 but two other studies were single blinded.37 62

Reported reasons for not including a placebo control and for not blinding subjects were: the expected bone loss if a placebo control was used,77 and the expected withdrawal bleeding in subjects who were initially amenorrhoeic taking OCs.3 96 The duration of the RCTs ranged from nine months73 to three years.21 30 The follow up rate was good, being >80% in one study, and 65% in another.62

The cohort studies included in this review were generally of good quality. In all of them, BMD was measured in the same way in both the OC exposed and non-exposed groups, and confounding variables were identified and accounted for. Further, the groups were similar.77 78 80 81 82 83 84 85 and the follow up rate was >80%.71 74 75 77 79 81 82 84 in most of the studies. However, in several of the studies, follow up was <80%.73 80 86 and the groups differed in factors potentially contributing to selection bias.62 65 66 67 68 69

Many of the studies reviewed were cross sectional.19 25 45–51 59–61 72 73 85–89 In addition, three case series19 78 90 and one case report71 were also reviewed. Evidence from these types of study is weaker, as confounding variables are less likely to have been controlled for, and the results may be more subject to selection and recall bias. Cross sectional studies and case reports are not specifically classified under the Oxford Centre for Evidence-Based Medicine levels of evidence; however, it was felt that they could provide useful evidence that should be included in this review.

A review by Kuohung et al86 evaluated 13 studies examining the effect of low dose OCs—that is, 20–40 μg ethinyl oestradiol—on BMD in women of all ages, including postmenopausal women. Their results suggested that there was fair evidence supporting a favourable effect of OC use on BMD.86 However, in premenopausal and perimenopausal women, there have been mixed results. Previous reviews have attributed these divergent results to differences in study design,95 96 inadequate sample sizes,95 97 and heterogeneity in study populations, because of the many confounders affecting BMD.2 4 such as genetics (race), lifestyle (smoking, alcohol, nutrition, exercise), and hormonal (menstrual history, age at menarche, parity, breast feeding) factors. There was a wide diversity in study populations examined among the papers reviewed, but we attempted to define more homogeneous populations by classifying studies into four groups according to health, menstrual status, and reproductive age (premenopausal or perimenopausal). However, an important distinction between reproductive age and skeletal age should be noted. As the average age of menopause ranges from 40 to 58 years,89 a woman classified as “premenopausal” can be anywhere from age 40 and below, and thus may be either skeletally immature or mature. Recker et al64 found that women do not reach skeletal maturity, as reflected by peak bone mass, until around 30 years of age. As skeletal maturity was not an inclusion criterion in any of the studies reviewed, it is unclear whether the subjects had attained peak bone mass or not. This heterogeneity in skeletal maturity may be partly responsible for the variability in results, especially in the cohort and cross sectional studies in healthy premenopausal women, where the evidence seemed to be split between positive effect and no effect. Interestingly, an RCT conducted in skeletally immature cynomolgus monkeys showed that OC treatment actually inhibited net bone accretion and/or growth by reducing bone metabolism,80 whereas no RCT in humans has yet shown a negative effect of OCs on BMD. Thus there is the potential that the effect of OC treatment on BMD may be, in part, dependent on skeletal (rather than reproductive) maturity.

Other factors affecting the results include the method and anatomic site of BMD measurement. Among the reviewed studies, there were seven different methods used:125I photon absorptiometry,19 39 single photon absorptiometry,64 82 83 86–90 computed tomography,19 39 single photon absorptiometry,64 82 83 86–90 computed tomography,28 41 74 dual photon absorptiometry,66 68 80 88 90 single x ray absorptiometry,66 69 77 79 90 and DXA.17 18 22 27 29 31–33 43–46 48 52 54 64 80 89 90 There were six different anatomic sites of BMD measurement: lumbar spine,16 20 23 25 27–29 31 33 34 35 38 40 42 44 45 46 48 51 54 56–62 66 67 69 72 74–79 81–83 86 88 90 hip (femoral neck, trochanter, Ward’s triangle),16 25 26 32 33 35 38 40–42 44 46 50 51 56–62 64 66 67 70 72 75 77 84 86 87 91 hand,34 35 37 42 44 46 51 52 58 64 72 73 75 76 radius,34 35 37 42 44 46 51 52 58 64 72 73 75 76 total body,24 25 32 33 35 36 40–42 44 46 48 50 51 56–62 64 66 67 69 70 72 75 77 84 86 87 91 This is important because the type of bone varies between anatomic site—for example, vertebral bodies are primarily trabecular, whereas the femur is predominantly cortical,96—and each method allows more accurate measurement of different types of bone—for example, DXA for trabecular, single photon absorptiometry for cortical.90 Furthermore, trabecular bone is more active than cortical; thus the effects of oestrogen may be more readily apparent in trabecular bone.4 Variations in location and method of BMD measurement may also account for previous discordant findings.

The type, dose, and formulation of OC used also differed between the studies reviewed. In two studies, mestranol was used,19 44 whereas in the rest, various doses of ethinyl

What is already known on this topic

- To date, there have been mixed results (either positive or no effect) in studies examining the effect of oral contraceptives and other hormone therapy on bone density in healthy premenopausal and perimenopausal women
- Previous reviews have not taken into account health or menstrual status

What this study adds

- This study reviews the evidence in premenopausal and perimenopausal women, including all study types (randomised controlled trials, as well as all other types)
- The studies are stratified according to health, menstrual status, and reproductive age, in order to more clearly define effects of oral contraceptives and other hormone therapy on bone mineral density in each group

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oestadiol were used (10 µg), 20 µg, 17 5 5 5 54 55 58 63 65 75 77 83 86 89 90
30 µg, 17 24 20 31 37 45 43 45 66 72 77 81 82 89
35 µg, 17 26 36 48 62 74 76 77 ≤50 µg, 47 56 57 58 70–100 µg, 19 45 64 65 78
or unknown/unspecified doses, 16 10–20 25 30–34 49–
51 59 69 70 72 73 80 85–89 91 and in combination with six different progestins or other hormones (levonorgestrel, 28 29 38 48 56 68 75 77 81
norgestrel, 7 29 38 57 78 85 norgestimate, 17 26 36 62 72 77 gestodene, 17 26 36 43 53 63 71 86 88
cyproterone acetate, 26 64 or drospirenone). 17 37). A study on postmenopausal women examining the effect of oestrogen dose on bone loss has suggested a dose-response effect: at <15 µg ethinyl oestradiol, net bone loss occurs, and at >25 µg
ethinyl oestradiol, net bone gain occurs, but between 15 and 25 µg ethinyl oestradiol, neither bone gain nor loss occurs. 101
If this dose-response effect holds true in premenopausal and
perimenopausal women, the doses used in some of the studies may have been insufficient to show any effect on BMD. In addition, different progestins vary in their effects on bone. 97 102 103 For example, one study showed that a portion of
norethindrone is converted into ethinyl oestradiol in the
body, resulting in potential bone-sparing properties. 104

The definition of OC exposure also differed greatly in the
cohorts and cross sectional studies. Some used the “non-user”
“user” distinction, 18 32–34 41 45 51–53 55–57 64–67 72 73 77 79 81–84 some
users. 16 25 30 50 Still others used specific time periods to define
OC users—for example, 16 25 30 50 months that OCs were used. Use of this
defined by multiplying the oestrogen dose per month by the
total number of months that OCs were used. Use of this
method in the future may make comparison
between studies easier.

CONCLUSION
There is good evidence for a positive effect of OCs on BMD in
premenopausal women, and fair evidence in “hypothalamic”
athletes in whom other conservative measures have not
resulted in return of normal ovulatory menses in a reasonable
amount of time, may be OCs. The “ideal” formulation(s) and
duration of treatment remain to be determined by further
longitudinal and prospective RCTs.

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controlled study on the influence of 2 oral contraceptives containing either
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