REVIEW

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

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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/amenorrhoeic premenopausal women. There is limited evidence for a positive effect in healthy and anorexic premenopausal women. In hypothalamic oligo/amenorrhoeic 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.

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According to Statistics Canada's 1996–1997 National Health Population Survey, 18% of Canadian women aged 15–49 use oral contraceptives (OCs).[1] In female athletes, OC use is at least as common as in the general population.[2] 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.[3] 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.[4] 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/amenorrhoeic, 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.[5] 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.[6] 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.[7] 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.[8]

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, oligomenorrhoea, and amenorrhoea). Ultimately, hypoestrogenism[9] and the nutritional deficits contribute to the development of decreased BMD. Management of the female athlete triad is multidisciplinary, involving doctors, psychologists, 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

Abbreviations: BMD, bone mineral density; DXA, dual energy *x* ray absorptiometry; IGF-I, insulin-like growth factor I; OC, oral contraceptive; RCT, randomised controlled trial

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 osteoblasts[11] and osteoclasts.[12] However, oestrogen also mediates indirect actions on bone through effects on hormones, such as calcitonin and parathyroid hormone, and on cytokines and growth factors.[13]

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 accretion.[14] 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 homoeostatic 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 progesterone 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 reviewed[16–90]: 11 RCTs,[26–29 62 63 69 74–76 80] 28 cohort,[16–18 30–38 55–58 64–68 70 77 79 81–84] 32 cross sectional,[19–25 39–53 59–61 72 73 85–89] three case series,[54 78 90] and one case report[71] (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 sectional[19–25]) showed a positive effect, 29 (four RCTs,[26–29] nine cohort,[30–38] 15 cross sectional,[39–53] one case series [54]) showed no effect, and seven (four cohort,[55–58] three cross sectional [59–61]) 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.[28] 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.[28] 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 1 Results from the electronic search strategies

MeSH or keyword	Medline	CINAHL	CDSR, ACP journal club, DARE, CCTR	SPORTDiscus
1 Bone Density (MeSH) or bone mineral density (keyword) or bone density (keyword)	22562	2288	2473	1123
2 Contraceptives, Oral (MeSH) or oral contraceptive (keyword)	34222	3649	809	197
1 and 2	351	212	30	18
Limit to English	327	212		17
Total	327	212	30	17

MeSH, Medical subject heading; CINAHL, cumulative index of nursing and allied health literature; CDSR, Cochrane database of systematic reviews; DARE, database of abstracts of reviews of effects; CCTR, Cochrane central register of controlled trials.

Table 3 Summary of articles reviewed

	Healthy premenopausal	Oligo/amenorrhoeic premenopausal	Anorexic premenopausal	Perimenopausal
Positive effect	–	2 RCTs	–	1 RCT
	3 Cohort	5 Cohort	–	4 Cohort
	7 X-sectional	–	2 X-sectional	3 X-sectional
Subtotal	10	7	2	8
No effect	4 RCTs	1 RCT	3 RCTs	–
	9 Cohort	1 Cohort	1 Cohort	–
	15 X-sectional	–	–	2 X-sectional
	1 Case series	–	1 Case series	1 Case series
Subtotal	29	2	5	3
Negative effect	–	–	–	–
	4 Cohort	–	1 Cohort	–
	3 X-sectional	–	–	–
	–	1 Case report	–	–
Subtotal	7	1	1	0
Total	46	10	8	11

RCT, Randomised controlled trial; X-sectional, cross sectional.

Table 4 Healthy premenopausal women: positive effect of oral contraceptives on bone mineral density

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
Cohort (level 2b,[16 18] level 4[17])	Recker *et al*[16]	156 college age women	Current OC users (n = 34) *v* past users (n = 43) *v* never	Forearm SPA; spine, total body DPA	Total body (but not forearm, spine) BMD positively correlated with OC use
	Berenson *et al*[17]	155 white, black, Asian, Hispanic women (ages 18–33) in the Armed Forces	35 μg EE+1 mg norethindrone (n = 28) *v* 30 μg EE+0.15 mg desogestrel (n = 35) *v* 150 mg DMPA (n = 33) *v* control (n = 59) for 12 months	Lumbar spine DXA	Increase in BMD in OC groups (norethindrone 2.33% increase in BMD; desogesterel 0.33% increase in BMD)
	Elgán *et al*[18]	118 women (ages 18–26)	Non-smoker/non-OC users (n = 35) *v* smoker/ non-OC user (n = 9) *v* non-smoker/OC user (n = 57) *v* smoker/OC user (n = 17)	Calcaneus DXA; urinary D-PYR	OC users had higher baseline and final BMDs; smoking was associated with a larger negative change in BMD than in non-smokers; overall, OC use moderated negative impact of smoking
Cross sectional	Goldsmith & Johnston[19]	2199 pre- and post-menopausal women (ages 15–79)	OC users (⩾100 μg mestranol, n = 332; <100 μg mestranol, n = 136; 50–100 μg EE, n = 83) *v* non-users (n = 1118)	Distal radius ^{125}I photon absorptiometry	OCs containing ⩾100 μg mestranol increase bone mineralisation (but OCs containing 50–80 μg mestranol or 50–100 μg EE did not)
	Lindsay *et al*[20]	57 women (ages 25–35)	Ever OC users (30 or 50 μg EE+norgestrel, n = 24) *v* never users	Lumbar spine DPA	12% higher BMD in ever OC users than in never users
	Kleerekoper *et al*[21]	2297 women (24% pre-, 76% post-menopausal)	29.7% ever OC users *v* 68.5% never OC users (1.8% missing)	Forearm SPA, lumbar spine DPA	Significant association between duration of OC use and BMD (greatest in those with ⩾10 years OC use)
	Laitinen *et al*[22]	293 Finnish women (186 pre-, 95 post- menopausal, 12 unknown; ages 20–76)	Premenopausal women: ever OC users (n = 65) *v* never users (n = 121)	Lumbar spine, proximal right femur DXA	Significant correlation between OC use and BMD in premenopausal women
	Pasco *et al*[23]	710 Australian women (511 pre-, 172 post- menopausal, 27 unknown; ages 20–69)	Ever OC users (n = 579) *v* never users (n = 131)	Lumbar spine, proximal femur, whole body, distal forearm DXA	3.3% greater mean lumbar spine BMD in premenopausal ever OC users than in never users
	Cobb *et al*[24]	476 black & white women (ages 18–30)	Lifetime month by month OC history by questionnaire (quantitative measure)	Spine, whole body, hip DXA	Significant correlation between spinal BMD and cumulative OC exposure in white but not black women
	Wallace & Ballard[25]	42 white women (ages 19–25)	Current OC users (n = 20) *v* non-users (n = 22)	Lumbar spine, total hip femoral neck, trochanter total body DXA	Significant correlation between trochanteric, total hip BMD and OC use

OC, Oral contraceptive; BMD, bone mineral density; SPA, single photon absorptiometry; DPA, dual photon absorptiometry; EE, ethinyl oestradiol; DMPA, deoxymedroxyprogesterone acetate; DXA, dual energy *x* ray absorptiometry; D-PYR, deoxypyridinoline.

Table 5 Healthy premenopausal women: no effect of oral contraceptives on bone mineral density

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
RCT (level 1b,[26 27 29] level 2b[28])	Castelo-Branco *et al*[26]	67 women (ages 19–29)	35 μg EE + 2 μg CA (n = 35) *v* 30 μg EE + 150 μg desogestrel (n = 32) for 24 months	DXA	No changes in BMD from baseline in either group
	Nappi *et al*[27]	60 women (ages 22–34)	20 μg EE +75 μg gestodene (n = 20) *v* 15 μg EE +60 μg gestodene (n = 20) *v* control (n = 20) for 12 months	Lumbar spine DXA; urinary PYR, D-PYR, serum osteocalcin	No changes in BMD from baseline in any group; decrease in PYR, D-PYR in OC treated groups suggesting decreased resorption
	Endrikat *et al*[28]	48 women (ages 20–38)	30 μg EE + 150 μg levonorgestrel (n = 25) *v* 20 μg EE +100 μg levonorgestrel (n = 23) for 36 months	Lumbar spine qCT; serum BSAP, urinary NTx	No changes in BMD from baseline in either group; decrease in NTx in both groups (suggesting decreased resorption)
	Nappi *et al*[29]	71 women (ages 22–34)	30 μg EE+3 mg drospirenone (n = 24) *v* 30 μg EE+75 μg gestodene (n = 24) *v* control (n = 23) for 12 months	Lumbar spine DXA; serum & urinary Ca^{2+}, serum osteocalcin, urinary PYR, D-PYR	Decrease in PYR, D-PYR in both OC treated groups from baseline (suggesting decreased resorption); trend to increased BMD in EE+drospirenone group
Cohort (level 2b)	Mazess & Barden[30]	300 women (ages 20–39)	50% past/current OC users, 50% never users	Lumbar spine DPA, radius SPA	No association between OC use and BMD
	Cromer *et al*[31]	48 women (ages 12–21)	30 μg EE + 150 μg desogestrel (n = 9) *v* Norplant (n = 7) *v* Depo-Provera (n = 15) *v* control (n = 17) for 12 months	Lumbar spine DXA	No significant difference between change in BMD in OC treated group (1.5% increase in BMD) *v* control (2.9% increase in BMD)
	Lloyd *et al*[32]	62 white women (followed from age 12–20 years)	OC users (''low dose monophasic'') (n = 28) *v* non-users (n = 34)	Proximal femur DXA	No effect of OC treatment on peak bone mass or rate of acquisition
Cohort (level 4,[33 34] level 2b[35–38])	Reed *et al*[33]	245 women (ages 18–39)	Current OC users (80% on 30–35 μg EE) (n = 89) *v* control (n = 156)	Lumbar spine, proximal femur, total body DXA	No change in BMD from baseline in either group
	Lara-Torre *et al*[34]	148 women (ages 11–21)	New OC users (n = 71) *v* new DMPA users (n = 58) *v* control (n = 19) over 24 months	Lumbar spine DXA	No change in BMD from baseline in OC users
	Lloyd *et al*[35]	80 women (ages 12–22)	OC users (for ⩾6 months, and still using at age 22) (n = 33) *v* non-users (n = 17)	Total body, bilateral proximal femur DXA	No difference in BMD between OC users and non-users
	Berenson *et al*[36]	191 women (ages 18–33)	OC (35 μg EE+1 mg norethindrone or 30 μg EE+0.15 mg desogestrel) (n = 86) *v* DMPA (n = 47) *v* control (n = 58) for 24 months	Lumbar spine DXA	No difference in BMD change from baseline between OC groups and control (decrease in BMD from baseline in DMPA group *v* control)
	Paoletti *et al*[37]	54 women (ages 20–30)	30 μg EE+3 mg drospirenone (n = 28) *v* control (n = 26) for 6 months	Heel DXA+laser; serum osteocalcin, BSAP, urinary PYR, D-PYR	No change in BMD from baseline in any group; decrease in osteocalcin, BSAP, PYR in OC group (suggesting decreased bone turnover)
	Rome *et al*[38]	370 women (ages 12–18)	20 μg EE+100 μg levonorgestrel (n = 165) *v* DMPA (n = 53) *v* control (n = 152) for 12 months	Lumbar spine, hip DXA; serum BSAP, urinary D-PYR	Increase in BSAP in control *v* OC, but no difference in BMD between groups
Cross sectional	Sowers *et al*[39]	86 women (ages 20–35)	OC users (for >2 months) (n = 78) *v* non-users (n = 8)	Bone mass by ^{125}I photon absorptiometry	No difference in bone mass between ever *v* never users or between current *v* past users
	Hreschyshyn *et al*[40]	352 women (pre- and post-menopausal; ages 24–79)	Ever OC users (n = 116) *v* never users (n = 236)	Lumbar spine, femoral neck DPA	No difference in BMD between ever OC users and never users
	Lloyd *et al*[41]	25 women	OC users (minimum 50 μg mestranol/day) (n = 14) *v* non-users (n = 11)	Lumbar spine qCT	No difference in BMD between OC users and non-users
	Stevenson *et al*[42]	284 white women (112 pre-, 172 post- menopausal)	OC users *v* non-users	Lumbar spine, proximal femur DPA	No association between OC use and BMD in premenopausal women
	Hall *et al*[43]	165 women (pre- and post-menopausal; ages4–80)	Ever OC users (n = 69) *v* never users (n = 96)	Lumbar spine DXA	No difference in BMD between ever OC users and non-users in any age group
	Murphy *et al*[44]	841 women (229 pre-, perimenopausal, 583 postmenopausal, 29 unknown)	Ever OC users (n = 159 pre-, perimenopausal; n = 182 postmenopausal; n = 11 unknown) *v* never users (n = 70 pre-, peri-menopausal; n = 401 postmenopausal; n = 18 unknown)	Lumbar spine, hip DXA	No difference in BMD between ever OC users and non-users

Table 5 (Continued.)

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
	Garnero *et al*[45]	208 women (ages 35–49)	OC users (combined pills with 30 μg EE, n = 41; combined pills with 50 μg EE, n = 3; sequential combined pills, n = 5; progestative contraceptives, n = 3) (total n = 52) *v* non-users (n = 156)	Lumbar spine, total body, hip, distal radius DXA; serum osetocalcin, BSAP, C terminal propeptide of type I collagen, urinary NTx and PYR	No difference in BMD between OC users and non-users; decrease in markers of both formation and resorption in OC users *v* non-users (suggesting decreased bone turnover)
	Ulrich *et al*[46]	25 women (mean age 41)	Ever OC users *v* never users	Axial, peripheral BMD by DXA	No difference in BMD between ever OC users and never users
	Petitti *et al*[47]	2474 women (ages 30–34)	Ever OC users (82% >30 but <50 μg oestrogen, 15% ⩾50 μg oestrogen, <1% <30 μg oestrogen, 2% unknown dose) (n = 819) *v* ever DMPA users (n = 350) *v* ever levonorgestrel users (n = 610) *v* control (n = 695)	Distal radius, midshaft ulna SXA	No difference in BMD between ever users of hormonal contraception *v* never users
	Ott *et al*[48]	227 women (ages 18–39)	OC users (53.6% 35 μg EE +0.5–1 mg norethindrone, 18% 35 μg EE + 1 mg levonorgestrel or 1 mg ethynodiol diacetate, 13.7% 30 μg EE +1.5 mg norethindrone, 9.7% 20 μg EE + levonorgestrel or norethindrone) (n = 39) *v* DMPA (n = 116) *v* control (n = 72)	Lumbar spine, total body, total hip DXA; serum Ca^{2+}, PTH, osteocalcin, urinary NTx	No difference in BMD between any of the groups; decrease in osteocalcin and NTx in OC users than in non-users (suggesting decreased bone turnover)
	Perotti *et al*[49]	189 women (ages 30–34)	OC users (for ⩾2 years) (n = 63) *v* DMPA users (for ⩾2 years) (n = 63) *v* control (no hormonal contraception) (n = 63)	Non-dominant radius SXA	No difference in BMD between any of the groups
	Hawker *et al*[50]	830 women (ages 19–35)	Current OC users (n = 223) *v* past OC users (n = 512) *v* never users (n = 95)	Non-dominant radius SXA	No association between OC use and BMD
	Wanichsetakul *et al*[51]	155 women (ages 30–34)	OC users (n = 59) *v* DMPA (n = 34) *v* control (n = 62)	Lumbar spine, femoral neck, Ward's triangle, greater trochanter, radius, ulna DPA	No difference in BMD between OC users and control
	Afghani *et al*[52]	39 Hispanic pre-/ peri-menopausal women (ages 22–51)	Current OC user *v* non-user	Whole body DXA	No relation between current OC use and BMD (but no info re duration of use, past use, dose, etc)
	Meyer *et al*[53]	61 women (40 athletes (19 eumenorrhoeic, 21 oligoamenorrhoeic) 21 eumenorrhoeic non-athletes; mean age 26 years)	Current OC user *v* non-user	Areal BMD of whole body, lumbar spine, proximal femur, femoral neck, greater trochanter	No association between OC use and areal BMD in athlete group
Case series (level 4)	Mais *et al*[54]	19 women (ages 20–30)	20 μg EE + 0.15 mg desogestrel for 12 months	Distal radius DPA; serum BSAP, urinary hydroxyproline:Cr	NS increase in BMD; decrease in BSAP, hydroxyproline (suggesting decreased bone turnover)

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

control groups choosing not to receive contraception,[27 29] which may have affected the validity of the results. No RCT showed a negative effect. But notably, two cohort studies[56 57] and one cross sectional study[59] 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.[14] However, Burr *et al*[56] 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. Similarly, Weaver *et al*[57] suggested that exercise in combination with OCs compromised attainment of peak spinal BMD. Hartard *et al*[59] reported that women with long term exercise and short term OC use had the highest lumbar spine and femoral neck BMD, whereas women with long term exercise and long term OC use had comparable BMD values to women with short term exercise and either long or short term OC use, suggesting that OCs offset the beneficial effects of exercise on BMD.

Oligo/amenorrhoeic premenopausal women

Ten studies on oligo/amenorrhoeic premenopausal women were reviewed. Menstrual irregularities were classified as ''hypothalamic'' oligo/amenorrhoea—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,[66] and from a variety of unspecified causes[65]). Although these conditions often occur in athletic females, as previously discussed, it is the energy

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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
Cohort (level 2b,[58] level 4[55–57])	Polatti *et al*[55]	200 women (ages 19–22)	20 μg EE+0.15 mg desogestrel (n=100) *v* control (n=100) for 60 months	Lumbar spine DXA; serum BSAP, urinary hydroxyproline:Cr	No change in BMD in treated group *v* increase in BMD in control group; no change in BSAP or hydroxyproline levels in either group
	Burr *et al*[56]	46 women (ages 18–31)	Non-exercisers/non-OC users (n=10) *v* non-exercisers + ⩽50 μg EE (n=13) *v* exercisers/non-OC users (n=8) *v* exercisers + ⩽50 μg EE (n=15)	Femoral neck DXA; serum osteocalcin, BSAP, acid phosphatase, urinary hydroxyproline:Cr	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
	Weaver *et al*[57]	179 women (ages 18–31)	Non-exercisers/non-OC users (n=40) *v* non-exercisers + ⩽50 μg EE (n=37) *v* exercisers/non-OC users (n=37) *v* exercisers + ⩽50 μg EE (n=40)	Lumbar spine, total body total hip DXA; radius SPA; serum osteocalcin, BSAP acid phosphatase, urinary hydroxyproline:Cr	Significant interaction between OC use and exercise, such that a combination of OC use and exercise compromises attainment of peak spinal BMD
	Cromer *et al*[58]	215 women (ages 12–18)	20 μg EE+100 μg levonorgestrel (n=79) *v* DMPA (n=29) *v* control (n=107) over 12 months	Lumbar spine, total hip, femoral neck, Ward's triangle, trochanter DXA	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
Cross sectional	Hartard *et al*[59]	128 women (ages 20–35)	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)	Lumbar spine, femoral neck DXA	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?
	Prior *et al*[60]	524 women (ages 25–45)	Ever OC users (for ⩾3 months) (n=454) *v* never users (0 to <3 months) (n=70)	Lumbar spine, proximal femur DXA	Decrease in lumbar spine, trochanter BMD in ever OC users *v* never users
	Hartard *et al*[61]	69 female endurance athletes (ages18–35)	OC group (use for >3years in women <22years old or use for >50% of time after menarche in women age 22–35) (n=31) *v* control (n=38)	Lumbar spine, hip DXA	OC users had 7.9% lower lumbar spine and 8.8% lower proximal femur BMD than control

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.

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) 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,[62 63] five cohort[64–68]) showed a positive effect, two (one RCT,[69] one cohort[70]) showed no effect, and one case report[71] 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 subjects.[65–71] Hergenroeder *et al*[62] showed an increase in total body and lumbar spine BMD with 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*[63] 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.[63] Conversely, Gibson[69] 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.[69] Further, the OC treated group in this study did show a non-significant increase in BMD after nine months.[69] No RCT showed a negative effect of OC treatment on BMD.

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)-IIIR or DSM-IV criteria (except for two studies,[73 79] in which the criteria used were not explicitly stated). Two cross sectional studies[72 73] showed a positive effect, five studies (three RCTs,[74–76] one cohort,[77] one case series[78]) showed no effect, and one cohort study[79] showed a negative effect. Klibanski *et al*[74] 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.[74] 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.[74] Gordon *et al*[75] 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.[75] Grinspoon *et al*[76] examined the effect of OCs, recombinant human insulin-like

Table 7 Oligo/amenorrhoeic premenopausal women: positive effect of oral contraceptives on bone mineral density

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
RCT (level 1b)	Hergenroeder *et al*[62]	24 women with hypothalamic amenorrhoea (ages 14–28)	35 μg EE+0.5–1 mg norethindrone (n = 5) *v* 10 mg medroxyprogesterone (n = 5) *v* placebo (n = 5) for 12 months	Lumbar spine, total body, femoral neck DXA	Increase in lumbar spine & total body BMD in OC treated group *v* placebo; no change in BMD at any site in medroxyprogesterone treated group
	Castelo-Branco *et al*[63]	64 women with hypothalamic oligomenorrhoea (ages 19–35)	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	Lumbar spine DXA	Increase in lumbar spine BMD in both OC treated groups; decrease in BMD in control group
Cohort (level 2b,[64 67 68] level 4[65 66])	De Creé *et al*[64]	11 sportswomen with athletic menstrual irregularity (ages 18–29)	50 μg EE+2 mg cyproterone acetate (n = 7) *v* control (n = 4) for 8 months	Lumbar spine DPA, radius SPA	9.5% increase in lumbar spine BMD in OC treated group
	Gulekli *et al*[65]	85 women with past (n = 33) or current (n = 52) history of amenorrhoea (ages 17–40)	Synthetic oestrogens (10–50 μg EE) (n = 40) *v* natural oestrogens (Premarin or oestradiol valerate) (n = 10) *v* 50 mg transdermal estradiol (n = 8) *v* bromocriptine (n = 9) *v* weight gain (n = 6) *v* control (untreated) (n = 12) for 3 years	Lumbar spine DXA	Increase in BMD in all treatment groups, but weight gain was most effective treatment; NS decrease in BMD in control group
	Haenggi *et al*[66]	21 women with hypothalamic or ovarian amenorrhoea, 123 healthy controls (ages 18–45)	30 μg EE+0.15 mg desogestrel (n = 15) *v* control (n = 123) for 24 months	Lumbar spine, proximal femur DXA	Initial BMD was lower in amenorrhoeic women than in healthy women; increase in lumbar spine, Ward's triangle BMD in OC treated group
	Cumming[67]	13 female runners with amenorrhoea (ages 23–34)	Oestrogen treated (0.0625 mg conjugated oestrogen (n = 6) or 50 μg transdermal estradiol (n = 2)) *v* control (n = 5) for 24 months	Lumbar spine, femoral neck, Ward's triangle DXA	Increase in lumbar spine, femoral neck BMD in oestrogen treated group; NS decrease in BMD in control group
	Rickenlund *et al*[68]	38 women (26 athletes (13 eumenorrhoeic, 13 oligoamenorrhoeic), 12 eumenorrhoeic non-athletes) (ages 16–35)	Each group received 30 μg EE+150 μg levonorgestrel for 10 months	Lumbar spine, total body DXA before and after 10 months of OC use	Increase in lumbar spine BMD in oligoamenorrhoeic athletes (especially those with low BMD at baseline); increase leg BMD in eumenorrhoeic athletes (related to weight-bearing exercise?)

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; EE, ethinyl oestradiol; 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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
RCT (level 2b)	Gibson[69]	34 women with athletic oligo/ amenorrhoea	Oestrogen treated (1 mg oestriol +2 mg oestradiol, days 1–12; 1 mg oestriol+2 mg oestradiol +1 mg norethisterone acetate, days 13–22; 0.5 mg oestriol+1 mg oestradiol, days23–28)+1000 mg calcium carbonate (n = 10) *v* 1000 mg calcium carbonate (n = 14) *v* control (n = 10) for 18 months	Lumbar spine, Ward's triangle, femoral neck, trochanteric region DXA	NS increase in BMD from baseline in oestrogen treated group
Cohort (level 2b)	Gremion *et al*[70]	30 female long distance runners (ages 19–37)	9 OC users, 10 eumenorrhoeic non-users, 11 oligo/ amenorrhoeic non-users over 12 months	Lumbar spine, proximal femur, midfemoral shaft DXA; osteocalcin	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

OC, Oral contraceptive; BMD, bone mineral density; RCT, randomised controlled trial; EE, ethinyl oestradiol; DXA, dual energy *x* ray absorptiometry; NS, non-significant.

Table 9 Oligo/amenorrhoeic premenopausal women: negative effect of oral contraceptives on bone mineral density

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
Case report	Zanker *et al*[71]	1 amenorrhoeic athlete (followed between age 24.8 to 36. 9 years)	For the first 5 years, used 30 μg EE+150 μg desogestrel	Lumbar spine, proximal femur DXA	9.8% decrease in lumbar spine BMD and 12.1% decrease in proximal femur BMD during 5 years of OC use

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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
Cross sectional	Seeman *et al*[72]	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)	OC users *v* non-users	Lumbar spine, total body, proximal femur DXA	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
	Karlsson *et al*[73]	366 women (77 non-OC users with AN, 58 OC users with AN, 26 women recovered from AN; 205 healthy controls)	OC users *v* non-users	Areal BMD by DXA, volumetric BMD calculated	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

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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/bone metabolism	Results
RCT (level 1b)	Klibanski *et al*[74]	48 women with AN (ages 16–42)	0.625 mg Premarin/5 mg Provera (n = 16) *v* 35 μg EE (n = 6) *v* control (n = 26) for 18 months	Lumbar spine CT	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 <70% *v* 20% decrease in BMD in control patients with initial ideal body weight of <70%
	Gordon *et al*[75]	51 women with AN (ages 14–28)	20 μg EE +0.1 mg levonorgestrel *v* 50 mg dehydroepiandrosterone for 12 months	Lumbar spine, total body, total hip, femoral neck, trochanter DXA; serum osteocalcin, BSAP, urinary NTx	NS increase in lumbar BMD in both groups; decrease in urinary NTx in both groups (suggesting decrease in resorption)
	Grinspoon *et al*[76]	60 women with AN	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, no OC) (n = 15) for 9 months	Lumbar spine, total body, distal radius, total hip, femoral neck DXA	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
Cohort (level 2b)	Golden *et al*[77]	50 women with AN (ages 13–21)	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 norgestrel) (n = 2), Lo-Estrin (30 μg EE + 1.5 mg norethindrone) (n = 2), Levlen (30 μg EE + 0.15 mg levonorgestrel) (n = 1), Alesse (20 μg EE + 0.1 mg levonorgestrel) (n = 1) (n = 22) *v* control (n = 28) for 36 months	Lumbar spine, left hip DXA	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
Case series (level 4)	Muñoz *et al*[78]	38 women with AN (mean age 17.3 years)	50 μg EE+0.5 mg norgestrel for 12 months	Lumbar spine DXA	No change in BMD from baseline

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.

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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
Cohort (level 2b)	Kreipe *et al*[79]	4 women with AN (ages 17–28)	Oestrogen + progestin replacement (n = 2) *v* control (n = 2) for 6 months	Lumbar spine DXA	1.9% decrease in BMD in oestrogen-progestin treated group *v* 1.3% increase in BMD in control group

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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
RCT (level 1b)	Volpe *et al*[80]	17 perimenopausal women (ages 46–53)	OC treated (n = 8) *v* control (n = 9) for 36 months	Spine DXA	NS increase in BMD in OC users, decrease in BMD in non-users
Cohort (level 2b,[81 83 84] level 4[82])	Shargil[81]	200 perimenopausal women (ages 41–49)	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	Lumbar spine, hand bone mass *x* ray/CT	No change in OC users *v* 6% decrease in BMD in controls
	Gambacciani *et al*[82]	32 perimenopausal oligomenorrhoeic women	30 μg EE+75 μg gestodene (n = 16) *v* 500 mg Ca^{2+} (n = 16) for 24 months	Radius DPA	Increase BMD with OC use
	Gambacciani *et al*[83]	90 perimenopausal (27 eumenorrhoeic, 54 oligomenorrhoeic) women	20 μg EE+0.15 mg desogestrel (n = 27) *v*500 mg Ca^{2+} (n = 27) for 24 months	Lumbar spine DXA	Increase in BMD with OC use *v* decrease BMD with calcium
	Gambacciani *et al*[84]	55 perimenopausal (18 eumenorrhoeic, 37 oligomenorrhoeic) women	20 μg EE+0.15 mg desogestrel *v* 500 mg Ca^{2+} for 24 months	Femoral neck, Ward's triangle, trochanter DXA	Increase in femoral neck BMD from baseline with OC use *v* decrease in femoral neck, Ward's triangle, trochanter BMD from baseline with calcium
Cross sectional	Enzelsberger *et al*[85]	200 perimenopausal women	>10years OC use (n = 30) *v* 2–9 years OC use (n = 50) *v* never use (n = 120)	Forearm SPA	OC use for >10 years associated with increase in BMD
	Tuppurainen *et al*[86]	3222 perimenopausal women	29% ever OC use	Lumbar spine, femoral neck DXA	Ever OC users had increase spinal BMD *v* never users
	Masaryk *et al*[87]	2038 women (98 peri-, 1940 post-menopausal)	18.3% ever OC use	Lumbar spine, hip DXA	Ever OC users had increase in spinal BMD *v* never users

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

Study design	Reference	No of patients	OC exposure	Measurement of BMD/ bone metabolism	Results
Cross sectional	Fortney *et al*[88]	352 perimenopausal women (ages 40–54)	Ever OC users (n = 260) *v* never users (n = 92)	Lumbar spine, radius DPA	NS increase in spinal BMD in OC users of longer duration and more recent use
	Beksinska *et al*[89]	496 perimenopausal women (ages 40–49)	OC users (30–40 μg EE) (n = 106) *v* DMPA (n = 127) *v* NET-EN (n = 102) (all for ⩾1year) *v* control (n = 101)	Distal radius, midshaft ulna DXA	No significant difference in BMD between any of the groups
Case series (level 4)	Volpe *et al*[90]	37 perimenopausal women (ages 45–48)	20 μg EE+150 μg desogestrel for 24 months	Lumbar spine DPA	NS increase in BMD (increase 8%)

OC, Oral contraceptive; BMD, bone mineral density; DPA, dual photon absorptiometry; NS, non-significant; EE, ethinyl oestradiol; DMPA, deoxymedroxyprogesterone acetate; NET-EN, norethisterone enanthate; DXA, dual energy *x* ray absorptiometry.

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

Study design	Reference	No of patients	OC exposure	Measurement of bone metabolism	Results
Oligo/amenorrhoeic					
RCT (level 1b)	Grinspoon *et al*[91]	45 women with hypothalamic amenorrhoea (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) *v* 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 al*[93]	41 women (ages 20–27)	30 μg EE+150 μg levonorgestrel (n = 21) *v* 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; bb genotype, no change. Control: no changes in any genotype
Cohort (level 2b)	Paoletti *et al*[94]	30 women (ages 22–30)	20 μg EE+75 μg gestodene (n = 10) *v* 30 μg EE+75 μg gestodene (n = 10) *v* control (n = 10) for 12 months	Urinary PYR, D-PYR	Decrease in PYR, D-PYR in OC-treated groups (suggesting decreased resorption)
	Kitai *et al*[95]	30 women (mean age 23.7 years)	OC users *v* non-users	Urinary Ca^{2+}/Cr ratio	Decrease in Ca^{2+}/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.

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 sectional[85–87]) supported a positive effect, whereas three (two cross sectional,[88 89] one case series[90]) showed no effect. Volpe *et al*[80] 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/amenorrhoeic 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/amenorrhoeic 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 group[91] (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 & Torstveit[92] 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 RCT[29] showed a non-significant trend towards increased BMD, and three RCTs[27–29] showed decreased concentrations of bone resorption markers in the OC group. Likewise, one RCT[93] and two cohort studies[94 95] 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,[56 57] suppression of endogenous pituitary releasing hormone, oestrogen, and progesterone peaks with resultant alteration

of the bone mechanostat,[59] and the differential effects of different progestins on BMD.[59]

According to the Oxford Centre for Evidence-Based Medicine levels of evidence,[15] 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 29 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[62 69 74 76 80] but only one was placebo controlled.[62] Only one study was double blinded,[28] but two other studies were single blinded.[27 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,[75] and the expected withdrawal bleeding in subjects who were initially amenorrhoeic taking OCs.[76] The duration of the RCTs ranged from nine months[76] to three years.[31 80] The follow up rate was good, being <80% in only two studies.[28 69]

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,[17 18 30–32 34 35 55–57 64 67 70 79 81–84] and the follow up rate was >80%[16 18 30–32 35 64 67 70 77 79 81 83 84] in most of the studies. However, in several of the studies, follow up was <80%,[17 33 34 55–57 65 66 82] and the groups differed in factors potentially contributing to selection bias.[33 65 66 77]

Many of the studies reviewed were cross sectional.[19–25 45–53 59–61 72 73 85–89] In addition, three case series[54 78 90] and one case report[71] 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 al*[96] 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.[96] However, in premenopausal and perimenopausal women, there have been mixed results. Previous reviews have attributed these divergent results to differences in study design,[4 97 98] inadequate sample sizes,[4 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,[99] a woman classified as ''premenopausal'' can be anywhere from age 40 and below, and thus may be either skeletally immature or mature. Recker *et al*[16] 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,[100] 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 anatomical site of BMD measurement. Among the reviewed studies, there were seven different methods used: ^{125}I photon absorptiometry,[19 39] single photon absorptiometry,[16 21 30 57 64 85 88] *x* ray/computed tomography,[81] quantitative computed tomography,[28 41 74] dual photon absorptiometry,[16 20 21 30 40 42 51 54 64 82 88 90] single *x* ray absorptiometry,[47 49 50] and DXA.[17 18 22–27 29 31–38 43–46 48 52 55–63 65 68 89] There were six different anatomical sites of BMD measurement: lumbar spine,[16 17 20–25 27–31 33 35 38 40 42 44 45 48 51 54 57–63 64 72 74–81 83 86–90] hip (femoral neck, trochanter, Ward's triangle),[22–25 32 33 35 38 40 42 44 45 48 51 56–62 66 67 69 70–72 75–77 84 86 87] hand,[81] heel,[37] radius,[16 19 21 23 30 45 47 49–54 76 82 85 88 89] and total body.[16 23–25 33 35 45 46 48 52 57 62 68 72 73 75 76] This is important because the type of bone varies between anatomical site—for example, vertebral bodies are primarily trabecular, whereas the femur is predominantly cortical,[62]—and each method allows more accurate measurement of different types of bone—for example, DXA for trabecular, single photon absorptiometry for cortical.[96] 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 32] 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

oestradiol were used (10 μg,[65] 20 μg,[38 54 55 58 63 65 75 77 83 84 90] 30 μg,[17 26 29 31 36 37 45 63 65 66 68 71 77 81 82 89] 35 μg,[17 26 36 48 62 65 74 76 77] ⩽50 μg,[47 56 57 81] 50–100 μg,[19 45 64 65 78] or unknown/unspecified doses,[16 18 20–25 30 32–34 49–51 59 60 70 72 73 79 80 85–88]) and in combination with six different progestins or other hormones (levonorgestrel,[28 38 48 56 68 75 77 81] norgestrel,[20 77 78] norgestimate,[77] norethindrone,[17 36 48 62 76 77] gestodene,[27 29 82] desogestrel[17 26 31 36 54 55 63 66 71 83 84 88] cyproterone acetate,[26 64] or drospirenone[29 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 cohort and cross sectional studies. Some used the ''non-user'' *v* ''user'' distinction,[18 32–34 41 45 51–53 55–57 64–67 72 73 77 79 81–84] some used ''ever'' *v* ''never'',[20–23 40 43 44 47 60 88] and others further subdivided ''ever'' users into ''current'' and ''past'' users.[16 25 30 50] Still others used specific time periods to define OC users—for example, >2 months,[39] ⩾6 months and still at the age of 22,[35] ⩾2 years,[49] ⩾4 years,[70] never/2–9 years/>10 years,[85] or >3 years if <22 years old or >50% of the time after menarche if >22 years old[61]—yet these time periods seemed arbitrary, as no reasons for their selection were given. Cobb *et al*[24] have suggested the concept of ''cumulative oestrogen exposure'' as a quantitative method of defining OC exposure, derived by multiplying the oestrogen dose per month by the total number of months that OCs were used. Use of this quantitative method in the future may make comparison between studies easier.

Clearly, a number of confounding variables influence the effect of OCs on BMD, which may contribute to the divergent results in the literature.

CONCLUSION

There is good evidence for a positive effect of OCs on BMD in perimenopausal women, and fair evidence in ''hypothalamic'' oligo/amenorrhoeic premenopausal women. However, there is limited evidence in anorexic and healthy premenopausal women for any positive effect. Further RCTs should be carried out to confirm these results. Ideally, any future studies would also take into account skeletal maturity, as well as reproductive maturity. In addition, studies of women with menstrual dysfunction should use consistent definitions of eumenorrhoea, oligomenorrhoea, and amenorrhoea.

Of significance to the female athlete is the combined effect of OCs and exercise on BMD, but to date there is a lack of evidence in this area. Ultimately, the decision to prescribe OCs to support BMD in the female athlete should be made on an individual basis, taking into account lifestyle and hormonal factors. Current literature does not show any evidence of a negative effect of OC use on BMD in women. OC use may have a favourable effect on BMD, especially in premenopausal women with athletic oligo/amenorrhoea. In these women, baseline BMD has been shown to be significantly lower than that in healthy controls; therefore the decision to treat is clinically more important. Hence, in oligo/amenorrhoeic athletes, the best therapeutic option to support BMD in those desiring contraception, or in those 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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