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Longitudinal changes in bone density in relation to oral contraceptive use

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Abstract

The primary aim of this 36-month prospective cohort study was to evaluate the association between use of oral contraceptives (OCs) and bone mineral density in reproductive-age women. The 36-month bone density (g/cm^2) at the spine, hip and whole body and percent change from baseline (measured at 6-month intervals) were evaluated among 245 women 18–39 years of age; 89 were using OCs (median duration: 3.7 years at study entry) and 156 were not using any hormonal contraception. Before and after adjustment for covariates (baseline bone density, age, race, ever pregnant, exercise, body mass and calcium intake), women using OCs did not differ significantly from comparison women in percent change in bone density over 36 months or in absolute bone density at 36 months. All *p*-values for between-group differences were >0.55 . In conclusion, within the limitations of this study, OCs did not appear to impact bone density over time in this cohort of reproductive-age women. © 2003 Elsevier Inc. All rights reserved.

Keywords: Bone density; Oral contraceptives; Longitudinal prospective

1. Introduction

Oral contraceptives (OCs) are the most common form of birth control among US women between the ages of 18 and 39 [1]. The decrease in both estrogen and progestin content in OCs over the past decade, especially in the more recent formulations of OCs, has led to a reduction in both side effects and cardiovascular complications, and potentially lower serum estrogen concentrations [2–4]. OCs inhibit ovulation and, consequently, women taking OCs do not experience the high mid-cycle concentrations of estrogen, >200 pg/mL , that occur with ovulation [3]. Average monthly serum concentrations of estradiol in OC users on preparations containing ≤ 35 μg of ethinyl estradiol range from 25–75 pg/mL [4]. These concentrations are similar to those seen in the early follicular phase of non-OC users, as compared to average monthly concentrations of approximately 120 pg/mL among ovulating women [3]. In addition to changes seen with estrogen, OCs increase the production and serum concentrations of sex hormone-binding

globulin, resulting in diminished concentrations of free testosterone and estrogen, an inhibition of gonadotropin secretion, and a further decrease in ovarian androgen secretion [5]. The shift toward lower-dose OC preparations could therefore potentially have a greater effect on bone mineral density due to a decreased concentration of circulating sex steroids. As estrogen and testosterone can profoundly affect bone metabolism [6,7], and both premenopausal and postmenopausal women with low estrogen concentrations are at increased risk for osteoporosis [8], the potential effect of current OC use on bone in premenopausal women is understandably of interest.

Relatively few longitudinal studies among menstruating adult women (aged <40 years) have investigated the association between OC use and change in bone mineral density, and results have been inconsistent [9–18]. Conflicting findings may be due in large part to the age of the participants, the estrogen/progestin doses in the OC preparations, the duration of the studies and anatomic sites evaluated.

We performed a prospective population-based study of young reproductive-age women, assessing bone mineral density over a 36-month period among current OC users and comparable women using no hormonal contraception.

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2. Materials and methods

This study was conducted at Group Health Cooperative, a large clinic and hospital-based nonprofit prepaid health plan in Washington State. The prospective study cohort was recruited from the greater Seattle area, between November 1994 and April 1996, and followed for up to 36 months.

Potentially eligible participants were women 18–39 years of age, randomly sampled from the enrollment database and chosen as comparison subjects for a larger study [19,20]. Participants were recruited and screened by telephone. Women were excluded if they were pregnant or planning to become pregnant, breastfeeding, were taking medications or had a condition known to alter bone mineral density. Women not using hormonal contraception (no use in the prior 12 months) and those currently using OCs were screened further for eligibility and willingness to participate. The study group consisted of 245 women, 89 using OCs at study enrollment and 156 not using any form of hormonal contraception.

Written informed consent was obtained from participants at the baseline clinic visit. All study procedures were reviewed and approved by the Group Health and University of Washington Human Subjects Committee. Study methods (exclusions, baseline measurements, significant confounding variables and questionnaire items) have been described previously [19]. Briefly, at the baseline visit, height and weight were measured, bone mineral density was assessed and the baseline questionnaire was reviewed. The questionnaire included items on demographics, reproductive history, current contraception, dietary intake [21], family history, exercise and lifestyle. Body mass index (BMI) was calculated as weight in kilograms per height in meters squared (kg/m^2). A computer-assisted personal interview was used to construct a contraceptive history prior to baseline. Additional information on the type of OC used was obtained from the health plan's pharmacy database. An index of weight-bearing physical activity over the past year was estimated by determining the frequency of 21 different types of activities, multiplying each by the level of weight-bearing (0–2) and summing the results for each participant. Repeat bone mineral density and follow-up questionnaires were completed every 6 months and food frequency questionnaires and indices of bone turnover were collected every 12 months, over the 36-month follow-up period [19].

Bone mineral density at the posterior-anterior lumbar spine (L1–L4), proximal femur (total hip), and whole body was measured at each visit using dual-energy absorptiometry (DEXA) (2 Hologic QDR 2000 densitometers; Hologic, Inc., Bedford, MA, USA). Each woman received all of her scans on the same densitometer. Our *in vivo* assessment of short-term reproducibility, the mean percentage difference of 1.8% for 15 duplicate hip measurements, was consistent with that reported in the literature [22]. The calibration system for one densitometer did not function up to study specifications for 2 of the 42 months in the study

period. The scans from this 2-month period ($n = 45$) were excluded from the analysis, with similarly proportional exclusions from both exposure groups. Replacement of the densitometer calibration system resulted in satisfactory calibration of the phantom (within 0.5%), but it caused a shift in the *in vivo* measurements by -0.74% , -1.39% and -2.24% for the spine, hip and whole body, respectively. Measurements taken after the densitometer repair were adjusted by these percentages.

We first examined baseline characteristics and tested for differences between the OC and comparison group using χ^2 tests for categorical variables (e.g., ethnicity and ever pregnant) and t-tests for continuous variables (e.g., daily calcium intake, physical activity level, BMI and bone mineral density). All t-tests were two-sided. Subjects were invited to come to each follow-up visit, even if they had missed prior visits. We calculated mean bone mineral density at each 6-month interval using all available data. Women who changed their baseline contraception status were excluded after their change, but data obtained until that point were included in the analyses.

We compared percent change in bone mineral density (g/cm^2), the primary outcome, from baseline to 36 months among OC users and women not using hormonal contraception. We also evaluated the absolute bone mineral density at 36 months. We had 80% power, $\alpha = 0.05$, to detect between-group differences as small as 1.05% at 3 years. We used a multivariable model to test for the effect of OC use on bone mineral density outcome measurements at 36 months, adjusting for baseline bone mineral density, age (18–21, 22–29, 30–39 years), ethnicity (white, non-white), ever pregnant, daily calcium intake, physical activity and BMI. The age categories were based on theoretical and known differences in bone metabolism in different age groups [11]. We used the same multivariable model to examine possible age-specific and weight-specific effects (<130 lbs, ≥ 130 lbs and women with BMI <22 kg/m^2 and ≥ 22 kg/m^2). The weight and BMI divisions were chosen based on the approximate lowest quartile among controls. These analyses were exploratory, as our numbers in the age and weight strata were small. All analyses were conducted using SAS (SAS Institute, Cary, NC, USA).

3. Results

Of the 245 eligible participants, overall follow-up was completed for 222 women (91%) at 12 months, 194 (79%) at 24 months and 178 (73%) at 36 months. Among the 89 women using OCs, 12-month follow-up was obtained on 80 (90%), 24-month follow-up on 69 (78%) and 36-month follow-up on 64 (72%); for the 156 women who did not use hormonal contraception, 12-month follow-up was obtained on 142 (91%), 24-month follow-up on 125 (80%) and 114 (73%) completed the 36-month follow-up. The principal reason for not completing the full 36 months was becoming

pregnant or attempting pregnancy (censored from further analysis). The second most common reason was moving out of the area. After excluding scans taken during the densitometer recalibration system replacement and accounting for changes in contraception (discontinuation of OCs among the OC-using group or initiation of any hormonal contraception in unexposed participants), data from 180 (73%) participants were included in the analyses at 12 months, 160 (65%) at 24 months and 134 (55%) at 36 months.

Most women (80%) used an OC containing 30–35 µg of ethinyl estradiol; the three most commonly used formulations were Norinyl 1/35, Brevicon and Tri-Levelen. Only one woman used a progestin-only pill. The median duration of OC use at entry to the study was 3.7 years with a range of 0.1 to 14.9 years. Women not using hormonal contraception were either not using contraception (37%), using barrier methods (29%), had an intrauterine device (3%), had a sterilization (tubal ligation or vasectomy) (26%) or used another form of contraception (17%). Some women used more than one method of nonhormonal contraception (10%).

At baseline, OC users were more likely than women not using hormonal contraception to be younger, white, never married, never pregnant and less active, have a lower BMI and take more calcium (Table 1). Between-group differences were significant for age, ever pregnant and physical activity ($p < 0.05$). Baseline hip, spine and total body bone densities did not differ between the two groups. During the 36-month follow-up, the unadjusted mean bone mineral densities were similar in both groups (Fig. 1). For the subgroup of women who had both baseline and 36-month visits and were not censored ($n = 134$), mean bone density change from baseline was also not different between OC and non-OC groups (data not shown).

Both before and after adjustment for covariates, women using OCs and comparison women did not differ significantly in change in bone mineral density over 36 months, and in absolute bone mineral density at 36 months (Table 2). Duration of OC exposure (<2 years, 2–4 years, ≥ 5 years) vs. no hormonal contraception did not alter this finding. The 36-month percent change from baseline in women using OCs was 0.48% at the hip, 1.61% at the spine and 0.68% for the whole body. Women in the comparison group had percent change from baseline of 0.12% at the hip, 1.34% at the spine and 0.66% for whole body (p -values for between-group differences = 0.55, 0.65, 0.96). Continuous users of OCs during the 36 months of follow-up had bone mineral densities of 0.952, 1.062, 1.100 g/cm² at the hip, spine and whole body, respectively. Women in the comparison group had bone mineral densities of 0.949, 1.059, 1.099 g/cm² at the hip, spine and whole body, respectively (p -values for between-group differences = 0.60, 0.73, 0.90).

Further evaluation of the association between OC use and bone density did not reveal significant age- or weight-specific effects (data not shown). However at 24 and 36 months, women 18–21 years of age who used OCs had a

Table 1
Study cohort baseline characteristics

	OC user		Non-OC user	
	N	(%)	N	(%)
No. of subjects	89	(100.0)	156	(100.0)
Age (y) ^a				
18–21	24	(27.0)	28	(17.9)
22–29	44	(49.4)	46	(29.5)
30–39	21	(23.6)	82	(52.6)
Race				
White	80	(89.9)	126	(80.8)
Black	4	(4.5)	5	(3.2)
Other	5	(5.6)	25	(16.0)
Education (y)				
≤ 12	11	(12.4)	18	(11.5)
> 12	78	(87.6)	138	(88.5)
Ever married	45	(50.6)	94	(60.3)
Ever pregnant ^a	32	(36.0)	79	(50.6)
Current smoker	17	(19.1)	30	(19.2)
Ever had amenorrhea	10	(11.2)	16	(10.3)
< 6 periods in last year	6	(6.7)	8	(5.1)
	Mean	(SE)	Mean	(SE)
Menarche age (y)	12.5	(0.2)	12.6	(0.1)
Weight (lbs)	151.3	(3.7)	157.6	(3.1)
BMI (kg/m ²)	25.1	(0.6)	26.3	(0.5)
Physical activity score ^a	70.9	(5.2)	85.6	(5.0)
Calcium intake (mg/day)	846.7	(52.5)	804.3	(42.1)
Total hip BMD (g/cm ²)	0.956	(0.014)	0.949	(0.010)
Spine BMD (g/cm ²)	1.043	(0.013)	1.046	(0.010)
Total body BMD (g/cm ²)	1.088	(0.009)	1.093	(0.007)

BMD = bone mineral density.

^a Test for difference between OC user and non-OC user, $p < 0.05$.

nonsignificant trend toward smaller percent change (smaller bone density gains) from baseline at all sites than similar-age participants not using hormonal contraception. This was not seen in older participants. In the analysis of weight, slender women (approximately the lowest weight quartile for comparison group women) using OCs had smaller bone density gains at all sites than the comparison group of similar weight (again, trends were nonsignificant).

4. Discussion

Our longitudinal study found that current OC use in this group of women ages 18–39 was not associated with absolute differences in bone mineral density or in the rate of bone mineral density change over 36 months. We did not see any marked differences between OC users and comparison women when we examined either the absolute mean bone mineral density at 36 months, or the percent change in bone mineral density between baseline and 36 months. Adjustment for the possible confounding effects of covari-

Fig. 1. Prospective mean bone mineral density for, (a) total hip, (b) spine and (c) whole body, by OC and non-OC user. Error bars represent 1 SE from the mean. —●— = OC user, --○-- = non-OC user.

ates and an evaluation of a possible duration-related change in bone mineral density also showed very little in the way of between-group differences at any anatomic site.

A woman who has had both of her ovaries removed is expected to lose approximately 11% of her bone density within a year [23] and a loss of nearly 5% over 6 months is estimated to occur among nursing mothers [24]. From 3 years before menopause until 3 years after menopause, spinal bone density decreases by approximately 10.5% [25]. Neither the OC nor the comparison groups experienced changes close to this magnitude; the current study with 80%

power, $\alpha = 0.05$, to detect between group differences as small as 1.05% at 3 years demonstrated no significant longitudinal differences between OC and comparison women.

There are relatively few longitudinal studies of the association of OC use with bone mineral density that have followed women for at least 3 years [9,11,12,18]. Similar findings to those reported here among women of comparable ages have been described in studies with varying lengths of follow-up, 5 years (spine) [9], 3 years (whole body) [18] and 2 years (spine) [10]. Others suggest that OC use among women of comparable ages to our study group for up to 5 years (whole body) [11] and for only 1 year (spine) [15] is associated with an increase in bone mineral density as compared with non-OC users. Several studies in adolescents and younger women demonstrated the converse: non-OC users accrued bone at the spine at a greater rate than OC users over a 5-year period in one study [12], and a 1-year, clinic-based prospective study showed bone mineral density increase at the spine was approximately half that among women using OCs as compared to the increase in the non-hormonal contraception comparison group, although this was not statistically significant [13]. Though all prospective, these studies varied in the components of the OC agents studied, the anatomic sites of interest, and in the age range of the study populations. Therefore, making comparisons among prospective studies is potentially problematic. In addition, secular differences in the OC formulations and changes in OC dosages over time, may make the findings from earlier studies less relevant to current clinical practices.

Three studies that analyzed the association of OC use with fracture risk as the outcome are also relevant [26–28]. All three studies suggest OC use in similar age women to those in our study may have an increased risk for subsequent fracture, including premenopausal fractures, when compared to women of similar ages not using OCs. The Royal College of General Practitioners Oral Contraceptive study [26] was a prospective cohort study of over 46,000 women (prevalent OC users and nonusers) with a mean age of 29 years at recruitment. They found that OC users experienced an increased risk of fracture after the age of 35 at all sites, except the forearm, as compared with never users [relative risk (RR): 1.2, 95% confidence interval (CI): 1.1, 1.3]. The analyses adjusted for parity, smoking and socioeconomic status and included all fractures diagnosed in hospitals in Great Britain. The Oxford-Family Planning Association contraceptive study [27] prospectively studied 17,302 women, ages 25–39, for 310,000 women-years of observation. Those women with current or recent use of OCs (RR: 1.3, 95% CI: 1.1, 1.5) or who used OCs for more than 2 years (RR: 1.2, 95% CI: 1.0, 1.5) had an increased risk of fracture as compared to women who never used OCs. Michaelsson and colleagues [28] conducted a large case-control study and showed that, for the subset of women who used OCs at age <30 years, there was a nonsignificant increased risk for fracture (RR: 1.3, 95% CI: 0.8, 2.1).

Table 2
Bone mineral density at 36 months (n = 42 OC users and n = 92 non-OC users)

Skeletal site	% Change in bone density from baseline			Absolute bone density (g/cm ²)		
	OC	Non-OC	p-value	OC	Non-OC	p-value
Crude results						
Hip	0.40	0.10	0.56	0.935	0.960	0.25
Spine	1.48	1.06	0.41	1.049	1.067	0.46
Whole body	0.66	0.39	0.44	1.084	1.106	0.13
Adjusted results ^a						
Hip	0.48	0.12	0.55	0.952	0.949	0.60
Spine	1.61	1.34	0.65	1.062	1.059	0.73
Whole body	0.68	0.66	0.96	1.100	1.099	0.90

^a Adjusted for baseline measures of bone mineral density, age (18–21, 22–29, 30–39), ethnicity (white vs. non-white), ever pregnant, daily calcium intake, weight-bearing physical activity and BMI.

Among women of all ages studied, those who had used a higher dose OC (50 µg ethinyl estradiol) were at the lowest risk for fracture (OR: 0.6, 95% CI: 0.4, 0.8) as compared to nonusers.

Our study has several strengths. We had an adequate number of participants to detect relatively small between group differences. Participants were enrolled members of a prepaid health plan, affording a population-based group of participants, rather than volunteers with possible associated study biases. While numerous cross-sectional studies on the association of bone mineral density and OCs in premenopausal women have been performed [17,29–33], relatively few have followed women prospectively for 3 years [9,11,12,18] as we did. Our ability to control for many factors known to affect bone mineral density and to utilize a prospective methodology should minimize potential bias. The measurement of bone mineral density at multiple anatomic sites strengthened interpretation of the results, as we were able to look for consistency among the various measurements. Lastly, the OC formulations used by our participants continue to be in widespread current use and therefore our findings are relevant and generalizable to women presently taking OCs.

Our study also had limitations. In an observational study of young women with OCs as an exposure, participants are apt to change their method of contraception and make new reproductive decisions over relatively short time spans. Thus, after censoring as participants changed their OC exposures, we had 36-month measurements on 134 (55%) of our initial participants. However, our overall follow-up at 36 months was very good (73%), and the decrease in numbers from censoring is less likely to introduce bias than would loss to follow-up of these participants. Data eliminated due to suboptimal function of one of the densitometers could potentially have been a source of bias, but this is unlikely, as small numbers of scans and similar proportions of data points were eliminated from both groups. We also could not control which OC formulations were used, which allowed for some heterogeneity in the exposure of interest. However, 80% of women were on formulations containing

30–35 µg of ethinyl estradiol and it seems unlikely that these differences would affect these findings.

In this 3-year prospective study of women age 18–39 years, the use of OCs was not associated with changes in bone mineral density. However, bone accrual peaks in the early 20s and critical bone remodeling occurs in the late teens and early 20s [11,34]. Register and colleagues [35] suggest that the effects of OCs on bone may differ for women who are actively gaining bone as opposed to women who have completed bone mass acquisition, based on research in the primate model. Our study group composition did not allow us to adequately examine this possible association in very young women using OCs, but further studies addressing the effect of OCs on bone mineral density in adolescents and young adult women may be important.

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