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Bone Mineral Density in Women Using Depot Medroxyprogesterone Acetate for Contraception

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Objective: To evaluate the possible effects of depot medroxyprogesterone acetate injectable contraception on bone mineral density in reproductive-age women.

Methods: We conducted a population-based cross-sectional comparison of bone mineral density levels in women using depot medroxyprogesterone acetate contraception and in women of similar age not using this method. The study recruited 457 nonpregnant women aged 18–39 years who were enrollees of a Washington state health maintenance organization. One hundred eighty-three women were receiving injections and 274 were not. Bone mineral density at several anatomic sites (spine, femoral neck, greater trochanter, and whole body) was measured using dual-energy x-ray absorptiometry. Data on other factors potentially related to bone density were collected through questionnaire and examination.

Results: Overall, age-adjusted mean bone density levels were lower for users of this method than for nonusers at all anatomic sites: The mean difference was 2.5% for the spine ($P = .03$) and 2.2% for the femoral neck ($P = .12$). Exposure to depot medroxyprogesterone acetate continued to be significantly ($P < .01$) associated with decreased bone density at the femoral neck, spine, and trochanter after multivariate adjustment for other risk factors related to bone density. Age-specific comparisons indicated that the major differences in bone density between users and nonusers occurred in the youngest age group (women 18–21 years); the mean femoral neck bone density was 10.5% lower ($P < .01$) for the exposed women, and differences were consistent ($P < .01$) across all anatomic sites. We also noted a significant dose-response relation between longer use of depot medroxyprogesterone acetate and decreased bone density levels in this age group ($P < .01$ for all sites).

Conclusion: These results provide evidence that contraception with depot medroxyprogesterone acetate, particularly long-term use, may adversely affect bone mineral density levels in young women aged 18–21 years. The implications for future bone health need further study. (Obstet Gynecol 1999;93:233–8. © 1999 by The American College of Obstetricians and Gynecologists.)

Depot medroxyprogesterone acetate, currently the most extensively used of the injectable contraceptives, has been in use for approximately 30 years in more than 90 countries.[1] Epidemiologic and clinical studies have evaluated this agent's safety, with generally reassuring findings.[2–7] Recently, however, Cundy et al[8] raised a potential concern in a cross-sectional study showing that long-term use of depot medroxyprogesterone acetate might adversely affect bone density in premenopausal women. Although provocative, this and the few other studies of this association to date have had limitations, principally in terms of the size and source of the study groups and consideration of other variables known to affect bone density.

We report the results of a population-based study of bone mineral density in a large cohort of reproductive-age women using depot medroxyprogesterone acetate for contraception and in comparable women not using this method.

Methods

These analyses are from the baseline data for an ongoing study of the effects of depot medroxyprogesterone acetate on bone density, which is being conducted at Group Health Cooperative of Puget Sound (Group Health). Located in western Washington state, Group Health is a nonprofit, group model health maintenance organization with approximately 500,000 enrollees.

Potential participants were identified from Group Health's computerized databases between November 1994 and April 1996. Each month, women aged 18–39 years who were receiving depot medroxyprogesterone

acetate injections for contraception were identified. All women who were new users of this method and a random sample of prevalent users were selected to make up the estimated required sample for the month, allowing for a 1:1.5 ratio of exposed to unexposed women. A comparison group of women who had not used this method was then selected randomly, frequency matching to exposed women on age and primary care clinic. Women who were pregnant, lactating, or trying to become pregnant were excluded. Because of the effects on bone density, we also excluded potential participants with a history of hysterectomy or oophorectomy, endometriosis, end-stage kidney or liver disease, metabolic bone disease, or cancer within the previous 10 years; as well as the use of steroids, anticonvulsants, or bisphosphonates. Women were also excluded if they planned to leave the area within the study follow-up period (2–3 years). Oral contraceptive (OC) use may be associated with increased bone density,[9] but exclusion on this very prevalent criterion among comparison women would have compromised their representativeness. Therefore, we chose to enroll a comparison group of sufficient size to address during analyses any differences in bone density among OC users and nonusers.

Written informed consent was obtained from each participant at the baseline examination. All study procedures were approved by the Human Subjects Committees at Group Health and at the University of Washington.

Upon entry into the study, participants completed a baseline questionnaire that included items on demographic characteristics, family history of osteoporosis and fracture, menstrual cycle information, pregnancy history, recent alcohol and caffeine consumption, current and past smoking habits, and physical activity levels. The Fred Hutchinson Cancer Research Center Dietary Intake Questionnaire, a food frequency questionnaire,[10] was used to assess calcium, protein, and other nutrient intake.

At the clinic visit, questionnaires were reviewed for completeness and height and weight were measured. Bone mineral density was measured using dual-energy x-ray absorptiometry (QDR 2000; Hologic Inc., Waltham, MA) at the proximal femur (femoral neck and greater trochanter), posterior-anterior lumbar spine (L1–L4), and whole body. Bone mineral density technicians were trained by Hologic and certified by the coordinating center for the Fracture Intervention Trial; they followed measurement protocols from that study.[11] We assessed reproducibility for the Group Health dual-energy x-ray absorptiometry machine and obtained duplicate hip measurements from 15 premenopausal women. The mean absolute percentage

difference was 1.8%, which is consistent with the approximately 2% difference reported in the literature for measurement at this site.[12,13]

At analysis, depot medroxyprogesterone acetate users and nonusers were first compared with respect to demographic variables and factors affecting bone mineral density levels (eg, age, ethnicity, weight, calcium intake, physical activity). Chi-square tests for categoric variables and t tests for continuous variables were used to evaluate the statistical significance of differences between the exposure groups.

Subsequently, we calculated age-adjusted mean bone mineral density levels in g/cm^2 for women using this method and for comparison women. We used t tests to examine between-group differences for each anatomic site. Average bone mineral density levels were also calculated for users and nonusers in five age categories (18–21, 22–25, 26–29, 30–34, and 35–39 years). The potential effects of varying durations of use were then evaluated within three age strata (18–21, 22–29, and 30–39 years) for the following intervals of use: less than 1–3 months, 4–6 months, 7–12 months, 13–24 months, and more than 24 months.

To evaluate more completely the potential effects of depot medroxyprogesterone acetate on bone density while accounting for the potentially confounding effects of other variables, we used least-squares linear regression models. Age and all variables that were significantly associated with both exposure status and with the outcome (mean bone density levels at any anatomic site) when considered univariately were entered into this model. Those variables that became nonsignificant were then removed to arrive at a final model.

Results

A total of 457 eligible women were enrolled in the study: 183 who were currently receiving depot medroxyprogesterone acetate injections and 274 comparison women. We contacted a total of 691 women who were receiving injections and 1159 potential comparison women. Of the women contacted who were found to be eligible (317 exposed and 473 unexposed women), 58% in each group agreed to participate and came for a baseline visit.

Table 1 summarizes the distribution, by exposure status, of demographic characteristics and factors affecting bone density. Compared with unexposed women, women exposed to this agent were significantly more likely to be nonwhite, to be current smokers, to be physically active, and to have less than a high school education. They were much more likely to have had a previous pregnancy (76.5% compared with 47.3%) and also reported having their first pregnancy at an earlier

Table 1. Study Sample: Selected Baseline Characteristics

Characteristic	DMPA exposed	DMPA unexposed
Total	183 (100.0%)	274 (100.0%)
Age (y)		
18–21	48 (26.2%)	62 (22.6%)
22–25	31 (16.9%)	43 (15.7%)
26–29	47 (25.7%)	59 (21.5%)
30–34	36 (19.7%)	58 (21.2%)
35–39	21 (11.5%)	52 (19.0%)
Ethnicity*		
White	132 (72.1%)	224 (81.8%)
Black	23 (12.6%)	17 (6.2%)
Asian	9 (4.9%)	16 (5.8%)
Other	19 (10.4%)	17 (6.2%)
High school education*	171 (93.4%)	269 (98.2%)
Employed	128 (69.9%)	205 (74.8%)
Never married	88 (48.1%)	123 (44.9%)
Smoking status*		
Current	55 (30.1%)	57 (20.8%)
Never	97 (53.0%)	178 (65.0%)
Past	31 (16.9%)	39 (14.2%)
Physical activity score		
0 to <40	42 (23.0%)	80 (29.2%)
40 to <80	48 (26.2%)	81 (29.6%)
80 to <120	28 (15.3%)	49 (17.9%)
120+	65* (35.5%)	64 (23.4%)
Fracture in female relative	30 (16.4%)	67 (24.5%)
Oral contraceptive use		
Current	0	94 (34.3%)
Past	163 (89.1%)	122 (44.5%)
Never	20 (10.9%)	58 (21.2%)
Ever pregnant*	140 (76.5%)	129 (47.3%)
Weight (lb)	157 ± 3.0	155 ± 2.2
Height (in)	65 ± 0.2	65 ± 0.2
Body mass index (kg/m^2)	26 ± 0.5	26 ± 0.4
Daily calcium intake (mg)	801 ± 41.8	803 ± 30.5
Age at first pregnancy (≥6 mo)*	22.1 ± 0.48	23.9 ± 0.51

DMPA = depot medroxyprogesterone acetate.
Data are presented as n (%) or mean ± standard error.
* $P < .05$.

age (mean 22.1 compared with 23.9 years). Women who had not used this method were more likely to report a family history of fracture.

The 183 exposed study-group members included both new and prevalent users of depot medroxyprogesterone acetate contraception. Duration of use ranged from 1 to 133 months. Forty-two women (23% of users) were seen within 1–3 months of use, 67 women (36%) within 4–12 months, 40 (22%) within 13–24 months, and 34 (19%) after 25 or more months of use. All exposed women were receiving the standard contraceptive dose (150 mg every 3 months).

Approximately 34% of our comparison women were current users of OCs. To assess whether OC users should be considered separately, we compared bone mineral density levels in this group with those for other women in the comparison group. After we adjusted for age, mean bone density levels for all anatomic sites were very similar between OC users and other comparison-group women; P values for differences ranged from .70 to .88. Our analyses, therefore, compare the entire group of unexposed women with those exposed to depot medroxyprogesterone acetate.

Overall, age-adjusted mean bone density levels for the lumbar spine were significantly lower among users of depot medroxyprogesterone acetate than among nonusers. Total mean bone density was 1.018 g/cm^2 for users and 1.044 g/cm^2 for nonusers (Table 2), a 2.5% difference ($P = .03$) (percent difference calculated as [bone density$_{unexp}$ − bone density$_{exp}$]/bone density$_{unexp}$). Differences in the same direction were seen for total mean bone density at the femoral neck ($P = .12$), greater trochanter ($P < .01$), and whole body ($P = .49$).

Age-specific comparisons showed that the largest differences between the exposed and unexposed women occurred in the youngest age group, women 18–21 years of age (Table 2). Differences were apparent at the spine (0.944 compared with 1.042 g/cm^2; $P < .01$) in users compared with nonusers, respectively (a 9.4% difference), and were similar in magnitude, direction, and significance ($P < .01$) at all other anatomic sites. In all other age groups, there were no significant differences in mean bone density levels at any anatomic site.

For the youngest women, we also noted a dose-response relation between longer duration of depot medroxyprogesterone acetate use and decreased mean bone mineral density levels (Figures 1 and 2). The trend was strongest for mean bone density at the femoral neck, where average values ranged from 0.841 g/cm^2 among women with 1–3 months of exposure to 0.736 g/cm^2 for women who had more than 24 months of exposure; the average value for nonusers was 0.893 g/cm^2 (P value for trend < .01). Similar trends, all significant and in the same direction, were seen for the other anatomic sites. These trends for differing durations of use were not seen in the older participants.

Univariate assessment of several baseline variables showed that age, race or ethnicity, history of fracture in a female relative, physical activity score, weight, height, body mass index (BMI), age at first pregnancy, and daily protein intake in grams were significantly associated ($P \leq .05$) with mean bone density levels for at least one anatomic site (data not shown). Smoking status was marginally associated with bone mineral density ($P = .06$) and was strongly associated with exposure status. These variables were entered in a multivariate model to consider the association between depot medroxyprogesterone acetate and bone density while controlling for the effects of these other factors. After removal of those variables that were not significant in the model (smok-

Table 2. Total and Age-Specific Bone Mineral Densities Among Women Exposed and Unexposed to Depot Medroxyprogesterone Acetate

Characteristic	18–21 y	22–25 y	26–29 y	30–34 y	35–39 y	Total mean BMD*
Number of subjects						
DMPA exposed	48	31	47	36	21	183
DMPA unexposed	62	43	59	58	52	274
Femoral neck BMD (g/cm²)						
Exposed	0.799 ± 0.013	0.869 ± 0.027	0.867 ± 0.017	0.832 ± 0.020	0.843 ± 0.035	0.838 ± 0.010
Unexposed	0.893 ± 0.016	0.841 ± 0.018	0.854 ± 0.017	0.856 ± 0.020	0.833 ± 0.016	0.857 ± 0.008
Test for difference (*P*)	<.01	.38	.60	.43	.78	.12
Trochanter BMD (g/cm²)						
Exposed	0.663 ± 0.013	0.719 ± 0.021	0.712 ± 0.014	0.694 ± 0.015	0.714 ± 0.026	0.696 ± 0.008
Unexposed	0.759 ± 0.015	0.701 ± 0.016	0.713 ± 0.013	0.728 ± 0.017	0.709 ± 0.013	0.724 ± 0.007
Test for difference (*P*)	<.01	.51	.97	.14	.87	<.01
PA lumbar spine BMD (g/cm²)						
Exposed	0.944 ± 0.012	1.041 ± 0.026	1.036 ± 0.018	1.024 ± 0.019	1.072 ± 0.023	1.018 ± 0.009
Unexposed	1.042 ± 0.017	1.019 ± 0.014	1.028 ± 0.017	1.077 ± 0.020	1.045 ± 0.013	1.044 ± 0.007
Test for difference (*P*)	<.01	.45	.73	.07	.30	.03
Whole-body BMD (g/cm²)						
Exposed	1.036 ± 0.009	1.092 ± 0.018	1.104 ± 0.012	1.088 ± 0.011	1.121 ± 0.021	1.085 ± 0.006
Unexposed	1.090 ± 0.010	1.074 ± 0.011	1.081 ± 0.011	1.109 ± 0.013	1.095 ± 0.011	1.091 ± 0.005
Test for difference (*P*)	<.01	.38	.18	.24	.24	.49

BMD = bone mineral density; DMPA = depot medroxyprogesterone acetate; PA = posterior-anterior.
Data are presented as mean ± standard error.
* Total mean BMD levels are age-adjusted.

ing and BMI), exposed women had significantly lower mean bone densities than unexposed women ($P < .01$) for the femoral neck, trochanter, and the lumbar spine (Table 3). Although in the same direction, differences were not significant for whole-body bone mineral density ($P = .13$).

Discussion

This study documents lower bone mineral density levels among users of depot medroxyprogesterone ac-

etate injectable contraception compared with similar women not using this method. The association with depot medroxyprogesterone acetate use was strongest in the youngest age group (18–21 years of age). In this group, we noted significant differences in bone mineral density between exposed and unexposed women for all anatomic sites. Further, a dose-response relation between duration of use and lower bone density was observed in the youngest users, and again the results were consistent across anatomic sites. Women who did and who did not use injectable contraception differed
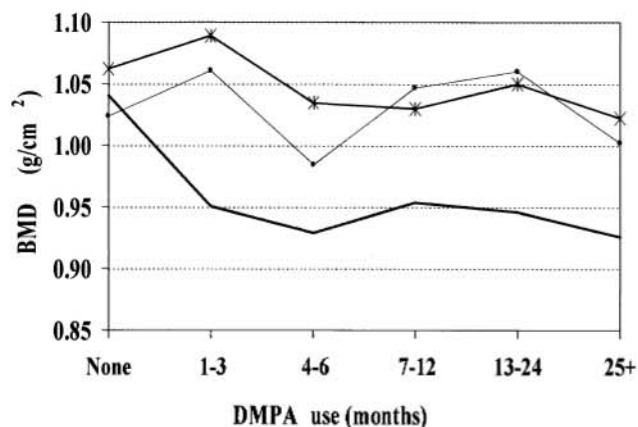

Figure 1. Age-specific bone mineral density (BMD) in the spine by duration of depot medroxyprogesterone acetate (DMPA) use. Age groups include 18–21 years (*solid line*), 22–29 years (*circles*), and 30–39 years (*crosses*). Trend for ages 18–21 is significant, $P < .01$.
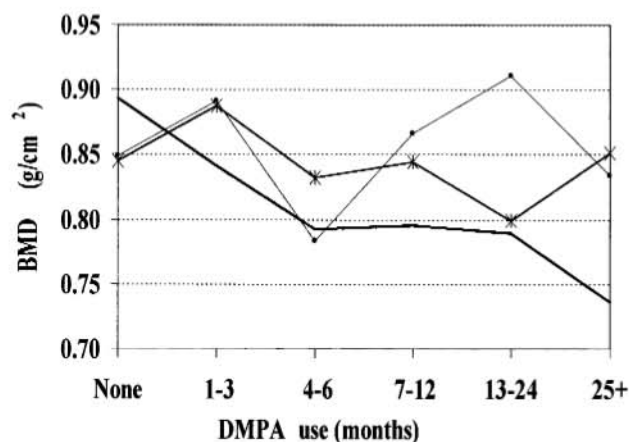

Figure 2. Age-specific bone mineral density (BMD) in the femoral neck by duration of depot medroxyprogesterone acetate (DMPA) use. Age groups include 18–21 years (*solid lines*), 22–29 years (*circles*), and 30–39 years (*crosses*). Trend for ages 18–21 is significant, $P < .01$.

Table 3. Adjusted Mean Bone Mineral Density Values by Exposure Status in a Multivariate Model*

Bone mineral density	DMPA exposed	DMPA unexposed	Test for difference (P)
Femoral neck	0.839 ± 0.012	0.868 ± 0.012	<.01
Spine	1.018 ± 0.011	1.050 ± 0.011	<.01
Trochanter	0.693 ± 0.010	0.722 ± 0.010	<.01
Whole body	1.093 ± 0.008	1.104 ± 0.008	.13

DMPA = depot medroxyprogesterone acetate.

Data are presented as mean ± standard error.

* The mean bone mineral density assumes a balanced design over all other covariates included in the model: age, ethnicity, weight, height, physical activity, age at first pregnancy (duration ≥6 mo), and history of fracture in a female relative.

most markedly in their pregnancy history. However, neither having been pregnant nor age at first pregnancy consistently affected hip or spine bone density levels. Moreover, in a multivariate model, associations for depot medroxyprogesterone acetate use were significant and independent of the effects of pregnancy history and other stronger correlates of bone density such as age, ethnicity, and weight.

Our findings are generally similar to those reported in earlier studies by Cundy et al[8] in that we noted lower bone densities among women who were exposed to depot medroxyprogesterone acetate than among comparison women. In their hospital-based cross-sectional study of 30 long-term users of this method and pre- and postmenopausal control women (also 30 per group), that study team reported a 6.6% (P = .002) lower average bone mineral density for the femoral neck and a 7.5% (P = .002) lower average for the spine among the cases when compared with the menopausal controls. In a second study by this group,[14] users of depot medroxyprogesterone acetate (n = 36) had average baseline bone density levels that were 5.7% (P > .05) lower at the femoral neck and 9.0% (P < .02) lower at the spine than levels in nonusers (n = 18). Although in the same direction, our overall age-adjusted differences between users and nonusers were less pronounced: We noted 2.2% and 2.5% differences in mean femoral neck and spine bone density levels, respectively (Table 2).

Our results differ most notably from these earlier data in showing significantly lower bone densities and a duration effect only among the youngest users of depot medroxyprogesterone acetate. The small size of the earlier studies[8,14] may well have precluded detailed examination of bone density levels by age and duration of use. Our study group also differs in other ways. Whereas we identified and actively recruited users of this method and comparable nonusers from a defined universe of health maintenance organization enrollees, earlier studies sought volunteers from family planning

clinics or hospital settings. Earlier studies also enrolled longer-term users of depot medroxyprogesterone acetate, whereas our purpose was to study the effects of a representative range of use. Consequently, women in the current study were considerably younger and had less exposure to this agent than earlier study groups.

Because of the cross-sectional nature of these data, we urge caution in attributing the differences that we report to use of this agent. To date, three small studies (with fewer than 20 women per group) have prospectively evaluated the actions of this method of contraception.[14–16] These studies have observed decreased bone density at the spine among depot medroxyprogesterone acetate users,[14,15] including adolescents, and increases in spinal bone density after discontinuation.[14] The one randomized trial[16] compared distal forearm bone density in women randomized to receive either depot medroxyprogesterone acetate injections or levonorgestrel implants. At 6 months, those treated with levonorgestrel experienced a nearly 3% increase in bone density, but those who used depot medroxyprogesterone acetate had a nonsignificant 0.41% decrease. Although these studies were conducted in small and select study groups, the two that assessed bone density changes after initiation of depot medroxyprogesterone acetate[15,16] have results consistent with the present study. The results after discontinuation of exposure, as reported by the New Zealand research group, are encouraging because they indicate some potential for recovery of lost bone mass at the spine.[14] However, there was less change in femoral neck bone density. In the youngest women in the present study, the notable percentage difference in mean bone density between depot medroxyprogesterone acetate users and nonusers was similar for the femoral neck (10.5%, 0.75 standard deviation [SD]) and spine (9.4%); these percentage differences were considerably higher than the percentage recovered after discontinuation by the New Zealand study subjects. If they persist, these differences are likely to be clinically important. After menopause, a 13% decrease in bone mineral density at the femoral neck (approximately 1 SD) is associated with a nearly threefold risk of hip fracture.[17]

The skeletal effects of depot medroxyprogesterone acetate were most pronounced in women aged 21 years and younger. A longitudinal study by Recker et al[9] of bone density changes in women in their third decade documented greater rates of bone gain in the younger women. Because the available evidence suggests that estrogen plays a critical role in attainment of peak bone mass,[18–21] it is likely that the effects of estrogen depletion—as occurs with the use of depot medroxyprogesterone acetate contraception[22,23]—may be greatest in women who are most actively acquiring bone mass (in

our study, women 18–21 years of age). This raises concern about the effects of this agent on bone density in younger adolescents, who are building bone at notably higher rates and who may favor this method over others.[24] At Group Health, approximately 12% of the women receiving these contraceptive injections during a recent 12-month period were under the age of 18.

Osteoporosis and the fractures accompanying low bone density are a major public health problem. Although prevention efforts to date have emphasized minimizing postmenopausal bone loss, factors influencing the attainment and maintenance of peak bone mass at younger ages also affect the future risk of fractures. Our examination of one such potential factor, the injectable contraceptive depot medroxyprogesterone acetate, was reassuring for women aged 22–39 years but showed a significant, duration-related association between its use and lower mean bone mineral density levels in women aged 18–21. More detailed prospective evaluation of the effects of depot medroxyprogesterone acetate use and discontinuation on rates of bone density change over time are needed to clarify the nature of this association and the degree to which it can be reversed.

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