Bone mineral density in adolescent females using injectable or oral contraceptives: a 24-month prospective study

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Objective: To determine whether bone mineral density (BMD) is lower in hormonal-contraceptive users than in an untreated comparison group.
Design: Observational, prospective cohort; 24-month duration.
Setting: Adolescent clinics in a metropolitan Midwestern setting.
Patient(s): Four hundred thirty-three postmenarcheal girls, 12–18 years of age, who were on depot medroxyprogesterone acetate (DMPA; n = 58), were on oral contraceptives (OCs; n = 187), or were untreated (n = 188).
Intervention(s): Depot medroxyprogesterone acetate and OCs containing 100 μg of levonorgestrel and 20 μg of ethinyl E_2.
Main Outcome Measure(s): Measurements of BMD at spine and femoral neck were obtained by using dual x-ray absorptiometry at baseline and 6-month intervals.
Result(s): Over 24 months, mean percentage change in spine BMD was as follows: DMPA, −1.5%; OC, +4.2%; and untreated, +6.3%. Mean percentage change in femoral neck BMD was as follows: DMPA, −5.2%; OC, +3.0%; and untreated, +3.8%. Statistical significance was found between the DMPA group and the other two groups. In the DMPA group, mean percentage change in spine BMD over the first 12 months was −1.4%; the rate of change slowed to −0.1% over the second 12 months. No bone density loss reached the level of osteopenia.
Conclusion(s): Adolescent girls receiving DMPA had significant loss in BMD, compared with bone gain in the OC and untreated group. However, the clinical significance of this finding is mitigated by slowed loss after the 1st year of DMPA use and general maintenance of bone density values within the normal range in the DMPA group. (Fertil Steril® 2008;90:2060–7. ©2008 by American Society for Reproductive Medicine.)

Key Words: Adolescents, oral contraceptives, bone mineral density, depot medroxyprogesterone acetate

Adolescence is a crucial period for skeletal development. Because of the dramatic effects of puberty on bone growth and consolidation, there is a up to a 50% increase in total body bone mass between the ages of 12 and 18 years (1). Because sex hormones play a key role in bone mass accrual, we were interested in the effects of hormonal contraception on bone in the growing adolescent (2, 3).

On November 17, 2004, the US Food and Drug Administration issued a so-called black-box warning that focused attention on young women by stating, "It is unknown if use of depot medroxyprogesterone acetate (DMPA) contraceptive injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk of osteoporotic fracture in later life" (4). Since that report, we have completed a 24-month observational study to observe the effects of DMPA on adolescent bone. Our hypothesis was that bone mineral density (BMD) would be significantly lower among DMPA users than among girls not using hormonal treatment.

Regarding oral contraceptives (OC), there has been a secular trend over the past 3 decades to decrease their estrogen content toward the minimum dose that still provides contraceptive efficacy but also minimizes the risk for thromboembolic events (5). However, because such events are exceedingly rare in the adolescent population (6), a potential

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concern is whether these lower-dose OCs provide enough estrogen for optimal bone accrual in very young women. Therefore, we also examined BMD over 24 months in adolescent girls who were using OCs containing 20 μg of ethinyl E_2, the lowest amount of estrogen that currently is available in the United States. Our hypothesis was that the gain in BMD among OC users receiving this level of exogenous estrogen would be significantly lower than that in the untreated group.

MATERIALS AND METHODS

Postmenarcheal girls, ranging in age from 12 to 18 years, were recruited from May 2000 through January 2003, from four general adolescent health clinics that were located in a metropolitan Midwestern setting. Adolescent girls initiating contraception with either DMPA or OCs were eligible for enrollment. Girls who attended these clinics over the same time period who did not plan to receive hormonal contraception during the 2-year observation period also were eligible for enrollment. Exclusion criteria included use of DMPA, pregnancy, or abortion within the past 6 months, use of OCs within the past 3 months, a chronic medical condition or treatment that could have an effect on BMD, contraindications to use of sex hormones, or a need for confidentiality in contraceptive management. The institutional review boards of all participating institutions approved the study. Written informed consent and assent were obtained from each custodial parent and study enrollee, respectively.

At baseline and at 6, 12, 18, and 24 months, clinical and behavioral information was obtained from each study participant. Clinical information was collected by direct interview and included menstrual bleeding patterns, general medical symptoms, and medication use. Height and weight were measured by using the same stadiometer (Easy Glide Bearing stature board) and Mettler-Toledo scale every visit. Gynecologic age was calculated as the number of years since menarche. Tobacco use was reported as current use or nonuse. Calcium intake was elicited with a focused 24-hour dietary recall, combined with the calcium Rapid Assessment Method (7). Girls who consumed <1,300 mg/d of dietary calcium were counseled by a dietician; if the level of intake did not improve after 3 months, the participant was given a sample of Tums (500 mg; GlaxoSmithKline, Philadelphia, PA) to be taken once per day for 3 months. Physical activity was assessed with a survey that asked each participant to classify herself as inactive, normal, or active.

At baseline and at 6, 12, 18, and 24 months, all study participants underwent measurement of BMD that included L1–L4 lumbar vertebrae, total hip (left), femoral neck, trochanter, and Ward's triangle. The measurement technique used was dual-energy x-ray absorptiometry, using the model QDR 4,500-W fan-beam densitometer (Hologic Inc., Bedford, MA). The software used was QDR for Windows 11.2 (Hologic), which included a low-density measurement option. In vivo intra-individual coefficients of variation were 1.2% at the spine and 1.4% at the femoral neck; inter-individual coefficients of variation were 1.3% at the spine and 2.2% at the femoral neck. All scans were obtained within 4 weeks of the scheduled 6-month intervals.

Because longitudinal growth typically does not conclude until late adolescence, we anticipated that skeletal size could change in our study participants over the observation period. As bones grow in width and length, bone thickness increases; increased bone thickness may falsely appear as increased bone density. Therefore, BMD was calculated by amount of scanned bone mineral content (BMC) within a projected area (Ap), termed areal density, and was expressed as grams per square centimeter. To correct for volumetric variations in bone, we performed an additional calculation to express bone mineral apparent density (BMAD), by using the following formulas:

$$\text{spine BMAD} = \text{BMC}\,(L_1\text{–}L_4)/\text{Ap}^{3/2} \text{ and}$$
$$\text{femoral neck BMAD} = \text{BMC}_{(\text{femoral neck})}/\text{Ap}^2_{(\text{femoral neck})} \quad (8)$$

Depot medroxyprogeserone acetate was administered every 12 weeks as a 150 mg, deep-IM injection (gluteus or deltoid). Girls in the OC group received an OC containing 20 μg of ethinyl E_2 and 100 μg of levonorgestrel. This particular pill was chosen because it contains the lowest dose of estrogen currently available in the United States. Compliance with DMPA injections was assessed by chart review and was calculated as number of injections divided by number of prescribed injections (total of 9 injections over 24 mo) $\times$ 100. Compliance rates with OC use were assessed by monthly self-report and were calculated as the number of pills taken, divided by the number of pills prescribed (1 pill per day from date of initiation, for 24 mo) $\times$ 100. Participants who elected to change contraceptive methods during the study were withdrawn.

Baseline characteristics and incidences of extreme bone loss were compared between groups with χ^2 tests or Fisher's exact tests for the categorical variables and analysis of variance or Kruskal-Wallis tests for the continuous variables. The association of changes in both BMD and BMAD over time was assessed in two ways. First, repeated-measures analysis of covariance was used, for which the time of the visit (baseline or 6, 12, 18, and 24 mo) was used as a factor in the model. Analysis of covariance also was used to examine the annual percentage change, for which the time factor was incorporated into the endpoint by calculating a percentage change in BMD or BMAD from baseline to 24 months. Before modeling, the distributional properties of continuous variables were examined for possible departures from normality. Multi-colinearity of predictors also was examined. The high correlation between chronological age and gynecologic age (Spearman $r = 0.69$, $P<.001$, n = 370) and between body weight and body mass index ($r = .94$, $P<.001$, n = 370) led to the decision to use only chronological age and body weight in the multivariate models to reflect an approach consistent with that of an analysis published elsewhere (3).