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Review article

Bone density recovery after depot medroxyprogesterone acetate injectable contraception use☆

Andrew M. Kaunitz[a,*], Raquel Arias[b], Michael McClung[c]

[a]Department of Obstetrics and Gynecology, University of Florida College of Medicine-Jacksonville, Jacksonville, FL 32209, USA
[b]Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA
[c]Oregon Osteoporosis Center, Portland, OR 97213, USA

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Abstract

Background: While depot medroxyprogesterone acetate (DMPA) is a highly effective contraceptive used by millions of women, its use is associated with bone mineral density (BMD) loss, raising concerns about long-term risk of osteoporosis and/or fractures.
Study Design: We conducted a systematic review of studies published in PubMed® from 1996 to 2006, evaluating changes in BMD after discontinuation of DMPA. Ten primary clinical or observational studies were identified addressing this issue.
Results: BMD consistently returned toward or to baseline values following DMPA discontinuation in women of all ages. This recovery in BMD was seen as early as 24 weeks after stopping therapy and persisted for as long as women were followed up; BMD in past DMPA users was similar to that in nonusers.
Conclusions: Bone loss occurring with DMPA use is reversible and is not likely to be an important risk factor for low bone density and fractures in older women, although data on fracture risk in DMPA users are lacking.

Keywords: Depot medroxyprogesterone acetate; Contraception; Injectable; Bone mineral density

1. Introduction

Depot medroxyprogesterone acetate (DMPA) is an injectable progestogen contraceptive that has been used worldwide for more than 40 years [1]. Effective and convenient, DMPA offers >2 million US women economical, long-acting, reversible hormonal contraception [1–5]. In December 2004, the US Food and Drug Administration (FDA) approved the lower-dose subcutaneous (SC) formulation (DMPA-SC 104 mg), which provides efficacy, safety and duration of action (3 months) equivalent to the older intramuscular (IM) formulation (DMPA-IM 150 mg) [6,7].

In recent years, observations of reduced bone mineral density (BMD) in current DMPA users have led to concerns that DMPA-induced bone loss might lead to osteopenia and increase the long-term risk of fractures — particularly in young women who have not yet attained their peak bone mass and among perimenopausal women who may be starting to lose bone mass [1]. The effect of DMPA on BMD is related to its contraceptive action: through inhibition of gonadotropin secretion, DMPA prevents follicular maturation and ovulation and causes endometrial thinning [8,9]. However, inhibition of gonadotropin secretion also results in suppression of ovarian estradiol production, and estrogen plays an important role in the regulation of bone density in premenopausal women [10,11]. Bone resorption via osteoclast activity is down-regulated by estrogens, and in hypoestrogenemia, bone resorption exceeds bone formation [11]. The imbalance between bone resorption and bone formation results in decreases in bone mineral density.

In 2004, the FDA required that a black box warning be placed on the DMPA package labeling that states, "Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely

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* Corresponding author. Tel.: +1 904 244 3109; fax: +1 904 244 3658.
E-mail address: andrew.kaunitz@jax.ufl.edu (A.M. Kaunitz).

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Table 1
Summary of studies assessing BMD recovery following discontinuation of DMPA

Study	Design	Age of subjects	*n* (DMPA)	*n* (Comparison group)	Duration of DMPA use	BMD sites	Key results
Postmenopausal women							
Orr-Walker et al. [37]	Cross-sectional	Mean, 60 years	34 (previous users)	312 (nonusers)	Median, 3.0 years (range, 0.2–18.1 years)	Whole body, lumbar spine, proximal femur	No significant differences between groups at any site
Cundy et al. [28]	3-year prospective observational	Mean, 50 years (range, 45–55 years)	16 (users until menopause)	15 (nonusers entering natural menopause)	Minimum of 5 years continuous use	Lumbar spine, femoral neck	Control group: 6% loss at both sites; DMPA users: little change ($p<.03$–$<.002$ between groups at Years 2 and 3)
Premenopausal women							
Cundy et al. [53]	Prospective observational	25–51 years	14 discontinuing users; 22 continuing users	18 nonusers	Median, 10 years (range, 3–20 years)	Lumbar spine, femoral neck	In subjects discontinuing DMPA use, lumbar spine BMD increased 3.4%/year ($p<.001$)
Petitti et al. [40]	Cross-sectional (international, multicenter)	30–34 years	350	695 (never used hormonal contraception)	≥24 months lifetime use (median, 36.4 months)	Distal radius, midshaft of ulna	No significant differences between past users and never users
Scholes et al. [15]	4-year prospective cohort	18–39 years	183 (110 who discontinued)	274 (nonusers)	Median, 11.3 months (range, 1–133 months)	Lumbar spine, proximal femur, whole body	Discontinuers had increases at both spine and hip (1.41%/year and 0.40%/year); at 30 months, mean BMD was similar to nonusers
Clark et al. [52]	4-year prospective longitudinal	18–35 years	178 (newly initiating)	145 (not using hormonal contraception)	Discontinuers: <12–36 months	Lumbar spine, total hip	<12 months of DMPA use: spine BMD increased 1.0%/year after discontinuation; 24–36 months: 1.9%/year; slower recovery of hip BMD
Kaunitz et al. [31]	7-year prospective matched cohort	25–35 years	248 (newly initiating)	360 (users of nonhormonal contraception)	Up to 5 years (240 weeks) of treatment and 2 years (96 weeks) posttreatment follow-up	Lumbar spine, total hip	At 96 weeks following discontinuation, total hip BMD returned to near baseline (mean, −0.2% change from pretreatment); partial recovery of lumbar spine BMD (−1.2% change from pretreatment)
Adolescents							
Scholes et al. [14]	3-year population-based prospective cohort	14-18 years	80 (DMPA users at baseline); 61 discontinued during follow-up	90 (age, similar; unexposed to DMPA)	Median, 12 months (range, 1–39 months)	Hip, spine and whole body	Discontinuers showed greater BMD increases vs. controls at all sites (hip, 1.34%/year; spine, 2.86%/year; whole body, 3.56%/year)
Women with endometriosis							
Schlaff et al. [46]	18-month randomized comparator-controlled clinical trial (North American)	18–49 years (premenopausal)	136 (DMPA-SC 104 mg)	138 (treated with leuprolide)	6 months (with 12 months of posttreatment follow-up)	Total hip, lumbar spine	After 6 months of treatment, DMPA-SC group showed significant reduction only in lumbar spine BMD (median change from baseline, −1.1%); after 12 months post treatment, no significant change from baseline in either total hip or lumbar spine BMD
Crosignani et al. [50]	18-month randomized comparator-controlled clinical trial (global)	18–49 years (premenopausal)	153 (DMPA-SC 104 mg)	146 (treated with leuprolide)	6 months (with 12 months posttreatment follow-up)	Total hip, lumbar spine	After 6 months of treatment, DMPA-SC group showed significant reduction only in lumbar spine BMD (median change from baseline, −1.0%); after 12 months post treatment, no significant change from baseline in either total hip or lumbar spine BMD