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What You Need to Know Labeling Issues for Depot Medroxyprogesterone Acetate

Millions of women worldwide, many in their teenage years, have been using the long-acting, injectable depot medroxyprogesterone acetate (DMPA; Depo-Provera®) for safe and effective contraception. Like other progestins, DMPA prevents ovulation, and, like breastfeeding, it reduces ovarian production of the hormone estradiol, leading to a temporary reduction in bone mineral density (BMD). Established research indicates that bone mineral density diminished during use recovers after discontinuation of DMPA.

In November 2004, the US Food and Drug Administration (FDA) issued “revised labeling” or a “black box warning” in the DMPA package labeling to highlight the fact that prolonged use may result in significant loss of bone density, that the degree of loss is proportional to the amount of time on DMPA, and that the loss may not be completely reversible.¹ The warning also indicates that a woman should use Depo-Provera for more than two years only if other contraceptive methods are inadequate for her.¹ This package safety warning also applies to new lower dose formulations of DMPA.

While the FDA seeks to inform health care providers and consumers of the concern that DMPA use during adolescence and early adulthood could negatively affect women during this critical period of bone accretion, critics charge that the warning is based on anecdotal reports, not the best science, and that the ultimate effect of such warnings is the needless discontinuation of a long-acting, convenient, safe, and effective contraceptive method with a subsequent rise in unintended pregnancies.² In the face of these concerns, an evidence-based review is in order.

What do we know about DMPA and its impact upon BMD and skeletal health?

As described above, DMPA users are likely to have a reduced BMD compared with non-users.³⁻⁶ Suppressed estradiol production is associated with an increased rate of bone resorption, and BMD consequently decreases in some DMPA users.^{4, 7-9} Observational research confirms that short-term diminishment of bone mineral density recovers within three years once DMPA is discontinued and that initial BMD diminishment has no known negative future impact upon skeletal health.¹⁰

DMPA use has not been linked to the development of menopausal osteoporotic fractures. Cross-sectional data from the World Health Organization (WHO) indicate that

women who formerly used DMPA had bone mineral densities similar to those of women who had never used it.¹¹ Regarding younger women, a large prospective cohort study of adolescents demonstrated a full recovery of BMD within one year after discontinuation of DMPA.¹²

Should health care providers offer “add-back estrogen” or serial dual-energy X-ray absorptiometry (DEXA) scans to young women on DMPA?

Two studies confirm that background estradiol levels mediate BMD changes in adult and adolescent DMPA users and that “add-back” estrogen prevents the transient decline in the bone mineral density of current DMPA users.^{13, 14} This research, however, also demonstrates that in both adult and adolescent women, BMD recovers after DMPA is discontinued, rendering it unlikely that women in either group would benefit from estrogen supplementation or serial surveillance by DEXA scans. In adolescents, regardless of contraceptive status, daily intake of 1500 mg of calcium and 400 mg of vitamin D is recommended to help achieve peak bone mass.

What are the WHO recommendations?

Currently, the WHO recommends that women in the age range of 18 through 45 years can use DMPA without restriction (WHO category 1). For women who are less than 18 or more than 45, the benefits of using DMPA generally outweigh the known or theoretical risks (WHO category 2).^{15, 16}

Conclusions

DMPA is a safe and effective contraceptive for adolescent as well as adult women. Use of DMPA should not routinely be restricted based on skeletal health concerns, because there is no evidence of increased fracture risk from the reversible and transient decreased BMD evident in DMPA users. Health care providers need to recognize that;

- The FDA’s black box label does not mandate serial BMD testing or the provision of “add-back” estrogen supplementation
- The current FDA guidance does not prohibit use of DMPA for more than two years. Existing data do not suggest the need to place any time limit on DMPA use for adolescents or women in general.

- For women who have additional risk factors for low BMD (such as cigarette smokers, women on chronic corticosteroids), supplemental use of menopausal doses of estrogen can be considered along with ongoing DMPA use. Examples of menopausal doses of estrogen include conjugated equine oral estrogen 0.625 mg daily, micronized oral estradiol 1 mg daily, and transdermal estradiol 0.05 mg patches.
- All women should consume age-based appropriate amounts of both calcium and vitamin D.

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1. www.fda.gov/medwatch/SAFETY/2004/DepoProvera_Label.pdf
 2. Kaunitz AM. Depo-Provera's black box: time to reconsider? *Contraception*. 2005;72(3):165-7.
 3. Cundy T, Evans M, Roberts H, Wattie D, Ames R, Reid IR. Bone density in women receiving depot medroxyprogesterone acetate for contraception. *BMJ*. 1991;208:13-16.
 4. Kaunitz AM. Injectable contraception: new and existing options. *Obstet Gynecol Clin North Am*. 2000;27:741-80.
 5. Banks E, Berrington A, Casabonne D. Overview of the relationship between use of progestogen-only contraceptives and bone mineral density. *BJOG*. 2001;108:1214-21.
 6. Westhoff CL. Depot-medroxyprogesterone acetate injection (Depo-Provera): a highly effective contraceptive option with proven long-term safety. *Contraception*. 2003;68:75-87.
 7. Depo-Provera Contraception Injection [product information]. Kalamazoo (MI): Pharmacia & Upjohn Company; 2004.
 8. Cundy T, Cornish J, Roberts H, Elder H, Reid IR. Spinal bone density in women using depot medroxyprogesterone contraception. *Obstet Gynecol*. 1998;92:569-73.
 9. Rome E, Ziegler J, Secic M, Bonny A, Stager M, Lazebnik R, et al. Bone biochemical markers in adolescent girls using either depot medroxyprogesterone acetate or an oral contraceptive. *J Pediatr Adolesc Gynecol*. 2004;17:373-7.
 10. Cundy T, Cornish J, Evans MC, Roberts H, Reid IR. Recovery of bone density in women who stop using medroxyprogesterone acetate. *BMJ*. 1994;308:247-8.
 11. Pettiti DB, Piaggio G, Mehta S, Cavioto MC, Meirik O. Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population: the WHO Study of Hormonal Contraception and Bone Health. *Obstet Gynecol*. 2000;95:736-44.
 12. Scholes D, et al. Change in Bone Mineral Density Among Adolescent Women Using and Discontinuing Depot Medroxyprogesterone Acetate Contraception. *Archives in Pediatric and Adolescent Medicine*. 2005;159:139-44.
 13. Cundy T, Ames R, Horne A, Clearwater J, Roberts H, Gamble G, et al. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. *J Clin Endocrinol Metab*. 2003;88:78-81.
 14. Kaunitz AM, Garceau RJ, Cromie MA; Lunelle Study Group. Comparative safety, efficacy, and cycle control of Lunelle™ monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum® 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). *Contraception*. 1999;60:179-87.
 15. World Health Organization. The Medical Eligibility Criteria for Contraceptive Use. 3rd ed. Geneva: WHO; 2004.
 16. World Health Organization. WHO Statement on Hormonal Contraception and Bone Health. Geneva:WHO;July 2005. Available at www.who.int/reproductive-health/family_planning/docs/hormonal_contraception_bone_health.pdf. Accessed on July 16, 2008.