

Canadian Contraception Consensus—Update on Depot Medroxyprogesterone Acetate (DMPA)

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Depot medroxyprogesterone acetate (DMPA) is a highly effective contraceptive method. It has been used as a contraceptive agent by millions of women in more than 90 countries since 1967 and was approved for use in Canada in 1997. Approximately 2% of Canadian women who are using contraception use DMPA as their birth control method.¹ In Canada, during a one-year period from October 2003 to October 2004, more than 629 000 prescriptions for DMPA were filled. Recent concerns about its effect on bone mineral density (BMD) have prompted advisories from the company that manufactures DMPA (Depo-Provera, Pfizer), the US Food and Drug Administration (FDA), and Health Canada.

Key Words: Bone mineral density, contraceptive agents, depot medroxyprogesterone acetate, osteoporosis, fractures, risk and benefits

DMPA has a number of advantages as a contraceptive agent. Because DMPA does not contain estrogen, it may be a suitable contraceptive option for women who have absolute or relative contraindications to estrogen, for example women with thrombophilias, female smokers over the age of 35, hypertensive women, and women who suffer from migraine headaches with associated neurological symptoms. DMPA has also been used to treat certain medical conditions, including menorrhagia, dysmenorrhea, endometriosis, and chronic pelvic pain. DMPA-associated amenorrhea is an advantage for women who prefer not to have menses because of menses-related symptoms, risk of anemia, or hygienic concerns. DMPA has the added advantage of demanding less compliance: because it is given as an intramuscular injection once every 12 to 13 weeks, it does not require daily attention and therefore may be more suitable for women who have difficulty adhering to other birth control regimens.

Frequently reported side effects with DMPA include menstrual cycle disturbances, headache,^{2,3} weight changes,⁴ and mood effects.² Amenorrhea occurs in 55% to 60% of DMPA users at 12 months.^{2,4–7} Although this is a reversible method of contraception, return of fertility may be delayed for an average of up to nine months.^{8–10}

A potential long-term consideration for women choosing DMPA is whether, by reducing BMD, DMPA adversely affects the future risk of fracture. There is increasing evidence that DMPA use results in, at least transiently, a decrease in BMD, probably because of the estrogen deficiency accompanying its use. Although some cross-sectional studies have demonstrated no adverse effect of DMPA on BMD,¹¹ the majority of studies report a decrease in BMD in DMPA users.^{12–21} Prospective studies have found mean losses of BMD at the lumbar spine of between 0.87% and 3.52%. The decrease in BMD appears to be proportional to the duration of DMPA use; the greatest

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Criteria for quality of evidence assessment and classification of recommendations

Level of evidence*	Classification of recommendations†
I: Evidence obtained from at least one properly designed randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination.
II-3: Evidence from comparisons between times or places with or without the intervention. Dramatic results from uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

*The quality of evidence reported in these guidelines has been adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on the Periodic Health Exam.³¹

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on the Periodic Health Exam.³¹

amount of loss is seen in new users,¹⁸ and the greatest rate of decrease occurs during the first two years of use.^{17,19,21} Although a variable decrease in BMD has been observed, it is not usually sufficiently large to cause the BMD to fall into the osteoporotic range. Furthermore, two cross-sectional studies of past DMPA users^{22,23} did not demonstrate a measurable difference in BMD compared with controls, suggesting that there is an improvement in BMD after DMPA is discontinued. Prospective studies have reported a substantial recovery of BMD once DMPA was discontinued, regardless of age.^{16,18} A similar effect on BMD is seen with lactation. The BMD of women who breastfeed for six months or longer can decrease by 4% to 5% but recovers to baseline once breastfeeding is discontinued.²⁴

Although published studies suggest that the loss of BMD is reversible, the interim results from as yet unpublished clinical studies prompted the FDA to issue a "black box warning" for DMPA in November 2004,²⁵ and in June 2005, Health Canada also issued an advisory.²⁶ The interim analysis found that in adult women who were on DMPA for five years, the decrease in hip and spine BMD was 5% to 6%. The decline was most pronounced in the first two years of use. When DMPA was stopped, BMD increased but did not always return to baseline in the first two years after discontinuation. Preliminary data in a small group of adolescents found a 2.44% to 6.53% decrease in BMD. As with the adult group, only partial recovery of BMD to baseline was seen during the two years of follow-up after discontinuation.

The DMPA-associated changes in BMD may be particularly important for adolescents, who are in the process of attaining peak bone mass. It is not clear whether the loss in BMD among adolescents prevents them from attaining their potential ultimate peak bone mass or if it will increase their risk of osteoporosis and fracture later in life. There is also concern regarding the perimenopausal DMPA user who may not have the opportunity to regain BMD before entering menopause with its associated accelerated phase of bone loss. The increase in fracture risk associated with a decrease in BMD has been studied in postmenopausal women, but there is little information on the effect of BMD changes on fracture risk for younger women, either during their younger years or later in life.

The World Health Organization (WHO), in its 2005 Statement on Hormonal Contraception and Bone Health, emphasizes that the critical outcome of interest with regard to bone health is the *occurrence of fracture*.²⁷ Although BMD measurements can be used to assess fracture risk, the accuracy of measurements can be affected by changes in body composition, and fracture risk is related to many factors besides BMD. It is not known whether DMPA-related BMD loss places women at increased risk for osteoporosis and fracture following menopause. Any potential effect will depend on a number of issues, including the magnitude and sustainability of loss, the microarchitectural deterioration of the skeleton associated with the bone loss, the level of BMD at the time of DMPA initiation, and the likelihood that other factors, such as physical activity, weight gain, and the development of comorbidities, affect this loss.¹⁹

Available data do not support routine BMD testing in DMPA users. In DMPA users with significant risk factors for osteoporosis, BMD testing may be appropriate, although the timing of initial testing and follow-up testing is controversial given the precision of the measurement. The smallest change that must be present before one can conclude with 95% confidence that the change is not related to measurement error is $2.77 \times \%$ coefficient of variation (CV). This is often called the least significant change, or LSC. In routine clinical settings the range of %CVs for lumbar spine is 1.8% to 2.3%; for femoral neck, 2.3% to 3.6%; and for total hip (which is now favoured for follow-up BMD measurement), 1.7% to 2.5%. Therefore, repeat BMD testing before two years is rarely indicated.²⁸

DMPA users should be counselled on aspects of "bone health," including calcium and vitamin D supplementation, weight-bearing exercise, decreased caffeine and alcohol consumption, and smoking cessation. Two studies have found that supplemental estrogen may attenuate the negative effects of DMPA on BMD^{29,30}; however, there are insufficient data to recommend this routinely or to recommend an appropriate dose of estrogen.

When discussing contraceptive methods, health care professionals, together with their patients, must weigh the risks and benefits of the various methods for each individual and discuss the many options that are available. DMPA is a highly effective contraceptive method and may be the best contraceptive option for some women, particularly those who are not able to take estrogen. DMPA may still be considered as a first-line contraceptive option, with no restrictions on its use or duration of use, in women aged 18 to 45 who have no contraindications. It appears that for many adolescents and perimenopausal women the advantages of using DMPA outweigh the theoretical concerns regarding fracture risk.

It is important that health care professionals and their organizations continue to keep abreast of research in this area and adjust their recommendations and practices accordingly.

SUMMARY STATEMENTS

1. DMPA use is associated with a decrease in BMD. This decrease appears to be most rapid in the first two years of use. The loss of BMD appears to be largely reversible once DMPA is discontinued. (Level I)
2. DMPA is associated with a decrease in BMD in adolescents during a critical period of bone accretion. BMD decrease during adolescence may result in ultimately lower peak bone mass. (Level I)
3. Available data do not support the routine use of BMD testing in DMPA users. In selected patients with signifi-

cant risk factors, BMD testing may be appropriate. BMD testing of DMPA users is best done in the context of a clinical study.

4. On the basis of current data, the advantages of using DMPA outweigh the concerns about its use by adolescent or perimenopausal women who have contraindications to, or difficulty using, other contraceptive methods. Research is needed to determine the long-term effects of DMPA use on BMD and future risk of fracture in adolescents and young adults.

Recommendations

1. Health care providers should inform patients of the potential effects of DMPA on BMD and counsel them on "bone health," including calcium and vitamin D supplementation, smoking cessation, weight-bearing exercise, and decreased alcohol and caffeine consumption. (Grade A)
2. SOGC endorses the WHO recommendation that "there should be no restriction on the use of DMPA, including no restriction on duration of use, among women aged 18 to 45 who are otherwise eligible to use the method." (Grade A)
3. The overall risks and benefits of continuing DMPA use should be discussed with DMPA users at intervals throughout the course of treatment. (Grade A)
4. SOGC does not recommend routine BMD testing in DMPA users. (Grade C)

REFERENCES

1. Fisher W, Boroditsky R, Morris B. The 2002 Canadian contraception study: part 1. *J Obstet Gynaecol Can* 2004; 26:580-90.
2. Schwallie PC, Assenzo JR. Contraceptive use—efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. *Fertil Steril* 1973;24:331-9.
3. Nelson A. Counseling issues and management of side effects for women using depot medroxyprogesterone acetate contraception. *J Reprod Med* 1996;41:391-400.
4. Polaneczky M, Guarnaccia M. Early experience with the contraceptive use of depot medroxyprogesterone acetate in an inner-city clinic population. *Fam Plann Perspect* 1996;28:174-8.
5. Betsey EM and Task Force on Long-Acting Systemic Agents for Fertility Regulation. Menstrual bleeding patterns in untreated women and with long-acting methods of contraception. *Adv Contracept* 1991;7:257-70.
6. Said S, Omar K, Koetsawang S, Kiriwat O, Srisatayapan Y, et al. A multicentred phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: 1. Contraceptive efficacy and side effects. World Health Organization Task Force on Long-Acting Systemic Agents for Fertility Regulation. Special Programme of Research, Development and Research Training in Human Reproduction. *Contraception* 1986;34:223-36.
7. Sangi-Haghpeykar H, Poindexter AN, Bateman L, et al. Experiences of injectable contraceptive users in an urban setting. *Obstet Gynecol* 1996;88:227-33.
8. Schwallie PC, Assenzo JR. The effect of depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: a review. *Contraception* 1974;10:181-202.

9. Pardthaisong T. Return of fertility after use of the injectable contraceptive Depo-Provera: up-dated data analysis. *J Biosoc Sci* 1984;16:23-34.
10. Fotherby K, Howard G. Return of fertility in women discontinuing injectable contraceptives. *J Obstet Gynaecol* 1986;6:S110-5.
11. Gbolade B, Ellis S, Murby B, Randall S, Kirkman R. Bone density in long term users of depot medroxyprogesterone acetate. *Br J Obstet Gynaecol* 1998;105:790-4.
12. Cromer BA. Bone mineral density in adolescent and young adult women on injectable or oral contraception. *Curr Opin Obstet Gynecol* 2003;15:353-7.
13. 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.
14. Scholes D, Lacroix AZ, Ott SM, Ichikawa LE, Barlow WE. Bone mineral density in women using depot medroxyprogesterone acetate for contraception. *Obstet Gynecol* 1999;93:233-8.
15. Berenson AB, Radecki C, Grady JJ, Rickert VI, Thomas A. A prospective, controlled study of the effects of hormonal contraception on bone mineral density. *Obstet Gynecol* 2001;98:576-82.
16. Scholes D, Lacroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: results from a prospective study. *Epidemiology* 2002;13:581-7.
17. Busen NH, Britt RB, Rianon N. Bone mineral density in a cohort of adolescent women using depot medroxyprogesterone acetate for one to two years. *J Adolesc Health* 2003;32:257-9.
18. Scholes D, Lacroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. *Arch Pediatr Adolesc Med* 2005;159:139-44.
19. Clark MK, Sowers MR, Nichols S, Levy B. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate. *Fertil Steril* 2004;82:1580-6.
20. Cromer BA, Stager M, Bonny A, Lazebnik R, Rome E, Ziegler, J et al. Depot medroxyprogesterone acetate, oral contraceptives and bone mineral density in a cohort of adolescent girls. *J Adolesc Health* 2004;35:434-41.
21. Lara-Torre E, Edwards CP, Perlman S, Hertweck SP. Bone mineral density in adolescent females using depot medroxyprogesterone acetate. *J Pediatr Adolesc Gynecol* 2004;17:17-21.
22. Orr-Walker BL, Evans MC, Ames RW, Clearwater JM, Cundy T, Reid IR. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal post-menopausal women. *Clin Endocrinol(Oxf)* 1998;49:615-8.
23. Pettiti DB, Piaggio G, Mehta S, Cravioto 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.
24. Sowers M, Corton G, Shapiro B, Jannausch ML, Crutchfield M, Smith ML, et al. Changes in bone density with lactation. *JAMA* 1993;269:3130-5.
25. US Food and Drug Administration. 2004. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01325.html>. Accessed September 6, 2005.
26. Health Canada. Drugs and Health Products, Advisories, Warnings and Recalls for Health Professionals. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/depo-provera_2_hpc-cps_e.html. Accessed September 6, 2005.
27. World Health Organization. WHO Statement on Hormonal Contraception and Bone Health. 2005. Available at: http://www.who.int/reproductive-health/family_planning/bone_health.html. Accessed September 6, 2005.
28. Khan AA, Brown J, Faulkner K, Kendler D, Lentle B, Leslie W, et al. Standards and guidelines for performing central dual X-ray densitometry from the Canadian Panel of International Society for Clinical Densitometry. *J Clin Densitom* 2002;5:435-45.
29. 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.
30. Cromer BA, Lazebnik R, Rome E, Stager M, Bonny A, Ziegler J, et al. Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who received depot medroxyprogesterone acetate for contraception. *Am J Obstet Gynecol* 2005;192:42-7.
31. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group;1994. p. xxxvii.