The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 602 • June 2014 *(Replaces Committee Opinion Number 415, September 2008)*
(Reaffirmed 2017)

Committee on Adolescent Health Care
Committee on Gynecologic Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Depot Medroxyprogesterone Acetate and Bone Effects

ABSTRACT: Depot medroxyprogesterone acetate (DMPA) is a highly effective injectable contraceptive that affords privacy and has a convenient dose schedule of four times per year, making it appealing to many users, especially adolescents. Although the use of DMPA is associated with loss of bone mineral density (BMD), current longitudinal and cross-sectional evidence suggests that recovery of BMD occurs after discontinuation of DMPA. No high-quality data answer the important clinical question of whether DMPA affects fracture risk in adolescents or adults later in life. The effect of DMPA on BMD and potential fracture risk should not prevent practitioners from prescribing DMPA or continuing use beyond 2 years. The potential health risks associated with the bone effects of DMPA must be balanced against a woman's likelihood of pregnancy using other methods or no method, and the known negative health and social consequences associated with unintended pregnancy, particularly among adolescents. Health care providers should inform women and adolescents considering initiating DMPA or continuing to use the method about the benefits and the risks of DMPA and should discuss the U.S. Food and Drug Administration "black box" warning and use clinical judgment to assess appropriateness of use.

Depot medroxyprogesterone acetate (DMPA) is an injectable contraceptive that has been used by approximately 1 in 5 adolescents and adult women in the United States who have had sex (1). Depot medroxyprogesterone acetate is a highly effective contraceptive that affords privacy (similar to an intrauterine system) and has a convenient dose schedule of four times per year, making it appealing to many users, especially adolescents. In a large cohort study of women and adolescents initiating contraception, unintended pregnancy rates for women using DMPA were similar to rates for women using intrauterine devices and implants and were significantly lower than rates for women using combined hormonal contraceptives (oral contraceptives, the contraceptive patch, or the vaginal ring) (2). In 2006, 49% of the 6.7 million pregnancies in the United States were unintended; unintended pregnancy rates were highest among women aged 18–19 years and 20–24 years (3). Limiting contraceptive options like DMPA may disproportionately affect adolescents and disadvantaged women.

Depot medroxyprogesterone acetate inhibits the secretion of pituitary gonadotropins, resulting in anovulation and decreased production of estrogen. Decreased estrogen production is of concern because it is associated with a decrease in bone mass or bone mineral density (BMD). In 2004, the U.S. Food and Drug Administration (FDA) added a "black box" warning to DMPA labeling about the potential loss of BMD (4), which might discourage health care providers from initiating DMPA or limit long-term use. Limiting the use of DMPA because of concerns over bone effects of DMPA would reduce contraceptive options for adolescents and other women for whom unintended pregnancy confers the greatest burden. The potential health risks associated with the bone effects of DMPA must be balanced against a woman's likelihood of pregnancy using other methods or no method, and the known negative health and social consequences associated with unintended pregnancy, particularly among adolescents (5).

Bone Mineral Density and Fracture Risk

Bone mass or BMD refers to the amount of mineral matter per volume of bones and directly correlates with bone strength (6). Bone mineral density is influenced by many factors, including, gender, age, race, body mass

index, hereditary factors, physical stress on bones related to physical activity and weight bearing, nutritional factors such as dietary calcium and vitamin D, alcohol consumption, smoking, corticosteroid exposure, and sex hormones and conditions that affect sex hormones (eg, pregnancy, breastfeeding, menopause, and use of hormonal contraceptives) (6). Peak bone mass is the amount of bone tissue present at the end of skeletal maturation. It is a major determinant of the risk of fracture due to osteoporosis because the mass of bone tissue at any time during adult life is the difference between the amount accumulated at maturity and the amount lost due to aging or other factors.

During puberty, the rate of accumulation of BMD at both the lumbar spine and femoral neck increases fourfold to sixfold over a 3-year period in females and then decreases rapidly after menarche. By 2 years after menarche, the rate of accumulation of BMD is insignificant (7). Studies of adult women demonstrate a decrease in BMD of 2–8% during pregnancy and 3–5% during breastfeeding (8, 9). These losses are temporary; within 6–12 months after giving birth or cessation of breastfeeding, BMD values increase to near preconception values in most women (10).

Depot Medroxyprogesterone Acetate Use and Bone Mineral Density

Cross-sectional and longitudinal studies using dual-energy X-ray absorptiometry (DXA) technology to evaluate current users of DMPA (aged 18–54 years) demonstrate lower BMD in DMPA users compared with nonusers, regardless of the anatomic site measured (11–18). Longitudinal studies report BMD losses of 0.5–3.5% at the hip and spine after 1 year of DMPA use (10, 12), a 5.7–7.5% loss in BMD after 2 years of use (16, 17), and 5.2–5.4% loss after 5 years of use (19).

Although the use of DMPA is associated with loss of BMD, current longitudinal and cross-sectional evidence suggests that recovery of BMD occurs after discontinuation of DMPA. The speed and completeness of BMD recovery differs by duration of DMPA use and by anatomic site (14, 16, 19, 20–23). In trials that included both adults and adolescents, with a duration of DMPA use of 2–5 years and follow-up of up to 5 years after discontinuation, losses in BMD appeared to be substantially or fully reversible; however, recovery at the hip and femoral neck generally took longer compared with recovery at the spine (14, 16, 19, 23, 24). In a study reviewed by the FDA from an open-label, nonrandomized, prospective multicenter study of 389 females aged 12–18 years with follow-up 5 years after discontinuation of DMPA, complete recovery in BMD at the spine, hip, and femoral neck was observed in adolescents who used DMPA for less than 2 years. However, complete recovery of BMD at the hip and femoral neck was not observed in all adolescents who used DMPA for 2 years or more (4). It is unknown if these changes in BMD observed in adolescents who received DMPA are clinically significant. Cross-sectional studies that demonstrated BMD in former adult DMPA users is similar to that of never users provides reassurance that loss of BMD associated with DMPA use is likely transient (25–27).

Depot Medroxyprogesterone Acetate Use and Fracture Risk

The clinical outcome of interest is the occurrence of fracture. Bone mineral density measurements and fracture have been best studied in postmenopausal women (6). Unlike for adult women, BMD has not been validated in adolescents as a marker of future fracture risk. No high-quality data answer the important clinical question of whether DMPA affects fracture risk in adolescents or adults later in life. In the United States, a prospective, cohort study of female military recruits and a cross-sectional study of girls and women with developmental disabilities found an increased risk of fractures in DMPA users; however, both studies had methodologic flaws that included selection bias and lack of information on potential confounders (eg, clinical information on range and severity of disability) that limit interpretation in the general population (28, 29).

Observational results from other countries provide mixed data on the association of DMPA use and fracture risk. A case–control study of women aged 20–44 years using the United Kingdom General Practice Research Database found an increased risk of fracture among women with current use of DMPA prescriptions compared with nonuse (odds ratio [OR], 1.36; 95% confidence interval [CI], 1.15–1.60; for women with 3–9 DMPA prescriptions and OR, 1.54; 95% CI, 1.33–1.78; for women with 10 or more DMPA prescriptions); however, when women with fractures potentially related to osteoporosis were considered, the risk of fracture for DMPA users (10 or more prescriptions of DMPA) was not significantly different compared with nonusers (OR, 1.49; 95% CI, 0.97–2.28) (30). In a cohort study of DMPA users also based on the United Kingdom General Practice Research Database, investigators found that DMPA users experienced more fractures than nonusers (crude incidence rate ratio for any fracture, 1.37; 95% CI, 1.29–1.45); however, before contraceptive use started, DMPA users had a higher incidence of previous fracture risk than nonusers, suggesting that the higher fracture risk observed may represent differences in fracture risk unrelated to DMPA use (31). In a population-based case–control study in Denmark, where all women with a fracture were compared with age-matched controls from the general population, DMPA use was associated with an increased risk of fracture (OR, 1.44; 95% CI, 1.01–2.06); however, the number of DMPA users in the population was small (n=163) and they were not able to control for potential confounders such as smoking and body mass index (32). Although these observational studies suggest a possible increased risk of fracture in

DMPA users, the results must be interpreted with caution because of inherent limits in study design.

The "Black Box" Warning

Concerns over the effect of DMPA use on BMD caused the FDA to issue a "black box" warning in November 2004 (4, 33). This warning stated that prolonged use of DMPA may result in significant loss of BMD, that the loss is greater the longer the drug is used, and that the loss may not be completely reversible after discontinuation. The warning notes that it is unknown if use of DMPA during adolescence or early adulthood will reduce peak bone mass and increase the risk for osteoporotic fracture in later life and cautions that use of DMPA beyond 2 years should be considered only if other contraceptive methods are inadequate. The FDA warning was based on independent analyses of data from clinical trials that indicated 1) the magnitude of the average decrease in BMD observed at the total hip and femoral neck were greater than decreases at the lumbar spine in adolescents with DMPA use for more than 2 years; 2) this decrease occurs at a time in life when adolescents normally experience a significant increase in BMD; and 3) there also was a lack of complete recovery of BMD at the hip at 5 years following 2 or more years of DMPA use. These findings are based on a small sample size of fewer than 50 adolescents.

In 2005, the World Health Organization convened a technical consultation on the effects of hormonal contraception on bone health (5). Experts reviewed extensive data on BMD changes in adolescents and considered the findings on changes in BMD and fracture risk in the context of the worldwide public health burden of unintended and adolescent pregnancy. They concluded that there should be no restriction on the use of DMPA in women aged 18–45 years, including no restriction on the duration of use. They also concluded that among females younger than 18 years and women older than 45 years, the advantages of using DMPA generally outweigh the theoretic safety concerns regarding fracture risk. Because data are insufficient to determine if BMD changes lead to increased fracture risk with long-term use, the overall risks and benefits of continuing use of DMPA should be reevaluated over time with the individual user (5).

Counseling

Health care providers should inform women and adolescents considering initiating DMPA or continuing to use the method about the benefits and the risks of DMPA and should discuss the FDA "black box" warning and use clinical judgment to assess appropriateness of use. The effect of DMPA on BMD and potential fracture risk should not prevent practitioners from prescribing DMPA or continuing use beyond 2 years. Individualized care and counseling is recommended for women with coexisting conditions that may influence bone health (eg, disabilities that increase risk of falls, chronic steroid use, renal disease, or malabsorption). Regular exercise, including weight-bearing exercise; smoking cessation; and age-appropriate calcium and vitamin D intake should be encouraged for all women. Although there have been no studies showing that these measures will offset loss of BMD during DMPA use, these recommendations can benefit general health. Adolescents should be counseled about other contraceptive methods and offered the option of initiating or transitioning to long-acting reversible contraceptive methods that have no effect on BMD, such as intrauterine devices and contraceptive implants, as alternatives to long-term DMPA use (34).

Management Considerations

Routine DXA for BMD monitoring is not recommended in adolescents and young women using DMPA because DXA has not been validated in these populations. Although studies of adolescents and women demonstrate that low-dose estrogen supplementation limits BMD loss in DMPA users (35, 36), estrogen supplementation during DMPA use also is not recommended because of potential adverse effects and a lack of evidence from clinical trials demonstrating effectiveness in adolescent populations for the prevention or treatment of fractures.

Conclusions

Based on currently available data, the American College of Obstetricians and Gynecologists' Committees on Adolescent Health Care and Gynecologic Practice make the following conclusions and recommendations:

- Depot medroxyprogesterone acetate (DMPA) is a highly effective injectable contraceptive that affords privacy (similar to an intrauterine system) and has a convenient dose schedule of four times per year, making it appealing to many users, especially adolescents.
- Although the use of DMPA is associated with loss of BMD, evidence suggests that losses in BMD appear to be substantially or fully reversible.
- No high-quality data answer the important clinical question of whether DMPA affects fracture risk in adolescents or adults later in life.
- The potential health risks associated with the bone effects of DMPA must be balanced against a woman's likelihood of pregnancy using other methods or no method, and the known negative health and social consequences associated with unintended pregnancy, particularly among adolescents.
- Health care providers should inform women and adolescents considering initiating DMPA or continuing the method about the benefits and the risks of DMPA and should discuss the FDA "black box" warning.
- Concerns regarding the effect of DMPA on BMD and potential fracture risk should not prevent

practitioners from prescribing DMPA or continuing use beyond 2 years.

- Routine DXA for BMD monitoring is not recommended in adolescents and young women using DMPA because DXA has not been validated in these populations.
- Adolescents should be counseled about other contraceptive methods and offered the option of initiating or transitioning to long-acting reversible contraceptive methods that have no effect on BMD, such as intrauterine devices and contraceptive implants, as alternatives to long-term DMPA use.

References

1. Mosher WD, Jones J. Use of contraception in the United States: 1982–2008. Vital Health Stat 23 2010;(29):1–44. [PubMed] [Full Text] ⇦
2. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med 2012;366:1998–2007. [PubMed] [Full Text] ⇦
3. Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. Contraception 2011; 84:478–85. [PubMed] [Full Text] ⇦
4. Pfizer. Letter to health care professionals. 2004. Available at: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM166395.pdf. Retrieved October 18, 2013. ⇦
5. World Health Organization. Technical consultation on the effects of hormonal contraception on bone health. Geneva: WHO; 2007. Available at: http://whqlibdoc.who.int/hq/2007/WHO_RHR_07.08_eng.pdf?ua=1. Retrieved February 12, 2014. ⇦
6. World Health Organization. Prevention and management of osteoporosis: report of a WHO scientific group. WHO Technical Report Series No. 921. Geneva: WHO; 2003. Available at: http://libdoc.who.int/trs/WHO_TRS_921.pdf. Retrieved February 12, 2014. ⇦
7. Bonjour JP, Rizzoli R. Bone acquisition in adolescence. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis. San Diego (CA): Academic Press;1996. p. 465–476. ⇦
8. Karlsson C, Obrant KJ, Karlsson M. Pregnancy and lactation confer reversible bone loss in humans. Osteoporos Int 2001;12:828–34. [PubMed] ⇦
9. 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. [PubMed] ⇦
10. Ulrich CM, Georgiou CC, Snow-Harter CM, Gillis DE. Bone mineral density in mother-daughter pairs: relations to lifetime exercise, lifetime milk consumption, and calcium supplements. Am J Clin Nutr 1996;63:72–9. [PubMed] [Full Text] ⇦
11. 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. [PubMed] [*Obstetrics & Gynecology*] ⇦
12. Berenson AB, Radecki CM, 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. [PubMed] [*Obstetrics & Gynecology*] ⇦
13. Wanichsetakul P, Kamudhamas A, Watanaruangkovit P, Siripakarn Y, Visutakul P. Bone mineral density at various anatomic bone sites in women receiving combined oral contraceptives and depot-medroxyprogesterone acetate for contraception. Contraception 2002;65:407–10. [PubMed] [Full Text] ⇦
14. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: results from a prospective study [published erratum appears in Epidemiology 2002;13:749]. Epidemiology 2002;13:581–7. [PubMed] ⇦
15. Berenson AB, Breitkopf CR, Grady JJ, Rickert VI, Thomas A. Effects of hormonal contraception on bone mineral density after 24 months of use. Obstet Gynecol 2004;103:899–906. [PubMed] [*Obstetrics & Gynecology*] ⇦
16. Clark MK, Sowers M, Levy B, Nichols S. Bone mineral density loss and recovery during 48 months in first-time users of depot medroxyprogesterone acetate. Fertil Steril 2006;86:1466–74. [PubMed] [Full Text] ⇦
17. 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. [PubMed] [Full Text] ⇦
18. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density: a systematic review. Contraception 2006;73:470–87. [PubMed] [Full Text] ⇦
19. Kaunitz AM, Miller PD, Rice VM, Ross D, McClung MR. Bone mineral density in women aged 25–35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. Contraception 2006;74:90–9. [PubMed] [Full Text] ⇦
20. 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. [PubMed] [Full Text] ⇦
21. 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. [PubMed] [Full Text] ⇦
22. Johnson CC, Burkman RT, Gold MA, Brown RT, Harel Z, Bruner A, et al. Longitudinal study of depot medroxyprogesterone acetate (Depo-Provera) effects on bone health in adolescents: study design, population characteristics and baseline bone mineral density. Contraception 2008;77: 239–48. [PubMed] [Full Text] ⇦
23. Harel Z, Johnson CC, Gold MA, Cromer B, Peterson E, Burkman R, et al. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. Contraception 2010; 81:281–91. [PubMed] [Full Text] ⇦
24. Kaunitz AM, Arias R, McClung M. Bone density recovery after depot medroxyprogesterone acetate injectable contraception use. Contraception 2008;77:67–76. [PubMed] [Full Text] ⇦

25. Petitti 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. [PubMed] [*Obstetrics & Gynecology*] ⇦

26. Orr-Walker BJ, 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 1998;49:615–8. [PubMed] ⇦

27. Viola AS, Castro S, Marchi NM, Bahamondes MV, Viola CF, Bahamondes L. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. Contraception 2011;84:122–7. [PubMed] [Full Text] ⇦

28. Lappe JM, Stegman MR, Recker RR. The impact of lifestyle factors on stress fractures in female Army recruits. Osteoporos Int 2001;12:35–42. [PubMed] ⇦

29. Watson KC, Lentz MJ, Cain KC. Associations between fracture incidence and use of depot medroxyprogesterone acetate and anti-epileptic drugs in women with developmental disabilities. Womens Health Issues 2006;16:346–52. [PubMed] [Full Text] ⇦

30. Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR. Use of depot medroxyprogesterone acetate and fracture risk. J Clin Endocrinol Metab 2010;95:4909–16. [PubMed] [Full Text] ⇦

31. Lanza LL, McQuay LJ, Rothman KJ, Bone HG, Kaunitz AM, Harel Z, et al. Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. Obstet Gynecol 2013;121:593–600. [PubMed] [*Obstetrics & Gynecology*] ⇦

32. Vestergaard P, Rejnmark L, Mosekilde L. The effects of depot medroxyprogesterone acetate and intrauterine device use on fracture risk in Danish women. Contraception 2008;78:459–64. [PubMed] [Full Text] ⇦

33. Pfizer Inc. Depo-provera CI (medroxyprogesterone acetate) injectable suspension, for intramuscular use: highlights of prescribing information. New York (NY): Pfizer; 2012. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=522. Retrieved February 12, 2014. ⇦

34. Hatcher RA, Trussell J, Nelson AL, Cates WJ, Kowal D, Policar MS. Contraceptive technology. 20th ed. New York (NY): Ardent Media; 2012. ⇦

35. 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. [PubMed] ⇦

36. 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 receive depot medroxyprogesterone acetate for contraception. Am J Obstet Gynecol 2005;192:42–7. [PubMed] [Full Text] ⇦

ISSN 1074-861X

Depot medroxyprogesterone acetate and bone effects. Committee Opinion No. 602. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:1398–402.