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Position paper

Depot Medroxyprogesterone Acetate and Bone Mineral Density in Adolescents—The Black Box Warning: A Position Paper of the Society for Adolescent Medicine

Abstract The purpose of this Position Paper is to review the published Black Box Warning regarding depot medroxyprogesterone acetate (DMPA) and bone loss as it relates to adolescent girls. The scientific findings that prompted the Food and Drug Administration to issue the warning are reviewed and the following additional issues are considered: (1) likely low risk of fracture related to DMPA use, (2) evidence of at least partial recovery after discontinuation of the method, and (3) the need to balance the physical, social and economic cost of adolescent pregnancy versus the immediate and long-term impact of DMPA on bone. A list of clinical guidelines is included, the main recommendation of which is to continue prescription of DMPA, with counseling about the risks and benefits, in most of the adolescent population desiring to use this contraceptive method.

Depot medroxyprogesterone acetate (Depo-Provera®, DMPA) is prescribed to over a million adolescent girls in this country annually. Its main use is for contraception; however, DMPA is also prescribed for menstrual cycle control in developmentally disabled patients as well as in patients with bleeding disorders because of its clinical side effect of amenorrhea. Due to the suppression of the pituitary-ovarian-uterine axis and consequent anovulation, DMPA has also been used in the management of severe dysmenorrhea and endometriosis. Other noncontraceptive clinical benefits from DMPA include protection against endometrial cancer as well as a reduction in sickle cell crises and seizures in these respective female patient populations.

As a highly effective form of contraception, DMPA is an appealing method for adolescent girls because it is easy to use (intramuscular injection at 12-week intervals) and can be used in private with no evidence of implants, pills, or patches. This method also is not intercourse-dependent and does not require partner involvement. Since its package insert was expanded to include labeling of DMPA for contraception in 1992, the increasing use of DMPA by adolescents has been credited, in part, with the decreasing numbers of adolescent pregnancies over the past decade in this country [1].

On November 17, 2004, the Food and Drug Administration (FDA) issued a black box warning regarding DMPA and its potential negative impact on bone mineral density, particularly as it relates to the adolescent. The warning indicates that "women who use Depo-Provera® Contraceptive Injection (DMPA) may lose significant bone density". . .which "may not be completely reversible." Furthermore, the warning focused attention on young women by stating, "It is unknown if use of Depo-Provera® Contraceptive Injection during adolescence or early adulthood, a critical period for bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture later in life" [2]. The purpose of this Position Paper is to first, briefly review the scientific findings that contributed to the regulatory agency's decision to formulate the black box warning. Second, we provide additional considerations that place potential bone density loss in a broader context including: (1) risk for current or future fracture, (2) the potential for recovery after discontinuation of DMPA, (3) bone strength, (4) short duration of DMPA use among adolescents, and (5) balancing risk versus benefit in comparing bone impact of DMPA with that of pregnancy. Finally, we provide a set of clinical guidelines for prescription of DMPA in adolescent girls that has been developed by the authors and endorsed by the Society for Adolescent Medicine.

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DMPA and bone mineral density

The pharmacologic action of DMPA results in suppression of the hypothalamic-pituitary-ovarian axis, creating a relative hypoestrogenic state. Bone metabolism, thus, resembles that of a normal peri-menopausal woman, with an expected loss in bone mineral density of around 1% to 3% per year, regardless of the age of the woman using DMPA [3–6]. An adolescent should normally be undergoing increases in bone mass at most anatomic sites. Any observed loss in bone density in this age group is of clinical concern, as such loss may result in compromised peak bone mass, a marker for future risk of osteoporosis. Of four prospective, observational studies including adolescents (age range 11–21 years) who received DMPA injections at 12-week intervals and untreated adolescents for up to two years, bone mineral density at the lumbar spine decreased a grand average of −3.1% (range −1.5% to −6.0%) compared with a grand average of +7.2% (range +5.9% to +9.5%) in untreated adolescents [7–10]. Thus, in these studies, the total average discrepancy in bone mineral density between DMPA users and untreated girls was 10.3%. A fifth prospective study in adolescents (aged 14–18 years) noted a drop of −5.0% at the spine among new DMPA users after 24 months versus +2.3% in untreated adolescents; at the hip, mean change was −6.1% versus −.9% (between-group differences of 7.3% and 5.2% for the spine and hip, respectively) [5]. If the effect of DMPA on bone is irreversible, discrepancies of this size may lead to a clinically significant difference in risk for fracture later in life. Thus, these findings lend support for the concern outlined by the FDA regarding loss in bone density in adolescent girls receiving DMPA.

Additional information in considering DMPA-associated bone loss

Fracture risk

Particularly germane to this discussion is whether DMPA increases the risk for current or future fracture. Although frailty fracture is the outcome of interest, these are rare in healthy premenopausal women. Thus, the focus of studies has been on the association between DMPA contraception and bone density as one potential indicator of fracture risk. Despite loss of bone mineral density in adolescents using DMPA, it is unlikely that girls would experience losses to the extent that would place them at immediate risk for fracture. To date, no studies have been published that assessed DMPA use and fracture risk in adolescent girls. Moreover, few studies have examined this issue in young adults. For example, Harkins et al, presented a case report of a young adult woman who experienced a large decrease in bone mineral density on DMPA and a tibial stress fracture [11]. In addition, Lappe et al, found an increased risk of stress fracture among non-Hispanic white female army recruits (mean age 21.1 + 3.7 years) with a history of DMPA use who were completing basic training (RR 1.71, 95% CI 1.0-2.9, p = .04) [12]. While the results of this study support other evidence suggesting bone loss, the authors note that, after adjustment for baseline bone density, the association was no longer statistically significant. This population also may not reflect the general population of adolescents.

Although there are no studies of DMPA use and risk of postmenopausal fracture, some have investigated bone density in older women after discontinuation of DMPA. Orr-Walker et al, in a small study of postmenopausal women (34/346 used DMPA), found that past use of DMPA was not associated with lower bone density at any anatomic site [13]. In this study population, the DMPA was prescribed at an average age of 41 years (28–50 years) and the median duration was 3.0 years. Petitti and colleagues also found no difference in bone density among adult women (aged 30–34 years) between past DMPA users, even long-term (> 4 years) users, versus never-users [14]. As bone density values were similar between past DMPA users and never-users, these cross-sectional studies suggest that a higher risk of fractures with past DMPA use would be unlikely. However, a direct assessment of fracture risk after DMPA use and, in particular, DMPA use during adolescence, is not available

Potential for bone mineral density recovery in adolescents after discontinuation of DMPA

A small number of prospective studies have evaluated bone recovery after discontinuation of DMPA. An initial study by Cundy et al found an increase of 3.4% in spinal bone mineral density in perimenopausal women who had discontinued DMPA one year before the measurement [15]. A number of subsequent longitudinal studies of adolescents also have demonstrated substantial recovery after DMPA discontinuation. Scholes et al, in a study of 457 women aged 18–39 years, with up to 36 months of follow-up, found that women who discontinued DMPA had significantly greater annualized mean bone density changes than comparison women (an average of +1.4% and +1.0% per year at the spine and hip, respectively, for DMPA discontinuers, vs. +.4% and −.1% in the comparison group). Of concern, hip bone density recovery was least complete in the youngest age category (ages 18–21 years; 23% of the cohort) in unadjusted assessments [6]. In a subsequent prospective study of 170 adolescents aged 14–18 years, mean annualized percent changes for the 38 DMPA discontinuers (with more than one measurement) were +2.9% and +1.3% at the spine and hip versus +1.3% and −.2% in the comparison group [5]. Adjusted bone mineral density values for DMPA discontinuers were at least as high as those of nonusers for all anatomical sites after 12 months discontinuation. In another longitudinal study of adolescents (n = 25, mean age 15.4 years) after use of DMPA (no comparison

group was included), bone mineral density of the spine increased +4.9% after 48 months post-cessation of treatment [16]. The data from all of these studies are encouraging, although it is unknown whether girls ultimately achieved the same peak bone mass as they would have in the absence of DMPA.

Last, a platform presentation at the 2005 annual meeting of the American College of Obstetricians and Gynecologists, Kaunitz and Kipersztok reported "substantial recovery" one year after discontinuation of DMPA in young adult women; however, 96 weeks postdiscontinuation, significantly lower values in bone density were still observed at the spine and hip between the discontinuers and never-users [17].

In summary, there is evidence of substantial recovery of bone density after discontinuation of use of DMPA. Whether full recovery occurs, especially in the very young adolescent (12–15 years), who is normally experiencing the highest levels of bone mass accrual, is unknown. The length of time required for recovery and the extent of recovery may vary according to duration of DMPA use and bone site. More studies are needed to better understand the factors that predict partial or complete recovery and whether particular adolescents, such as those with a family history of osteoporosis, low weight or immobilization, are at particular risk of long-term effects.

Bone strength

It is increasingly clear that bone mineral density, usually measured with dual X-ray absorptiometry (DXA), is insufficient to fully express a bone's ability to withstand external stress (i.e., to resist fracture). Moreover, DXA does not provide information about changes in bone geometry as a result of hormone (or any other form of) treatment. An important factor in determining bone strength is its geometric shape. Research in postmenopausal women has shown that, although their bone mineral density decreases dramatically with the loss of estrogen, bone strength is much less compromised due to an additional thin rim of bone added to its external surface [18]. Biomechanical theory indicates that the farther away from the central axis this new bone is placed, the more strength is conferred. To assess bone geometry, one either has to employ indirect formulae for special DXA views or apply peripheral quantitative computed tomography [19,20]. These measurements are relatively new to the field of bone research, and have not been applied to young women with hypoestrogenism such as those on DMPA; therefore, we do not yet know the effects of estrogen deficiency on bone strength and geometry in the growing adolescent.

Short duration of use of DMPA among adolescents

A potentially mitigating factor in adolescent DMPA users relates to duration of use. Adolescents typically use DMPA as contraception for brief periods of time, with over 50% deciding to discontinue use by one year [21]. Such brief exposures of bone to the drug effect would seem likely to predispose to resumption of normal bone development, and data on recovery in short-term users are encouraging. Thus, adolescent girls' bone may be protected both with short-term use due to both brief exposure to the drug and speedy recovery of normal bone metabolism. However, other girls using DMPA for contraceptive and noncontraceptive purposes (e.g., menstrual hygiene) may elect to continue the medication for years, and thus, studies of long-term use are particularly relevant for the adolescent.

Balancing risk versus benefit in comparing bone density loss and benefit of effective contraception

It is perhaps most important to consider balancing the risk: benefit ratio of bone loss versus the need in certain adolescents for a highly effective and user-friendly method of contraception. In this balance, one must take into account the multiple psychosocial and physiologic consequences, including potential impact on bone of possible pregnancy resulting from ineffective contraception. The sparse data that are available suggest that bone mineral density decreases during pregnancy in adolescents [22], despite increases in body weight and high circulating levels of sex hormones, factors well known for their positive impact on bone. This effect on the maternal skeleton may be due to the large calcium needs of the fetus in the presence of typically poor calcium dietary intake of the pregnant teen, thereby inducing secondary hyperparathyroidism and bone resorption in the mother. Thus, caution is urged for clinicians when considering stopping DMPA in the adolescent who is otherwise at high risk for pregnancy. The risks and benefits are likely to have a different ratio when considering noncontraceptive uses of DMPA.

Suggested guidelines for practitioners

The Society for Adolescent Medicine endorses the following guidelines for clinicians who prescribe DMPA for their adolescent patients:

Continue prescribing DMPA to adolescent girls needing contraception with adequate explanation of benefits and potential risks. The recent World Health Organization statement suggested no restriction of the use of DMPA for women aged 18 to 45 years who are otherwise eligible to use the method: "Among adolescents (menarche to <18) and women over 45, the advantages of using DMPA generally outweigh the theoretical safety concerns regarding fracture risk. Because data are insuffi-

cient to determine if this is the case with long-term use among these age groups, the overall risks and benefits for continuing use of the method should be reconsidered over time with the individual use" [23]. The risk of bone loss should be balanced with the clinical indication for this method of contraception, alternative methods, and specific circumstances of each patient. For example, a clinician may want to continue (or initiate) prescribing DMPA to an adolescent who is otherwise at high risk of pregnancy that, in turn, has its own risk for bone loss. The risk benefit ratio may be altered when considering DMPA for noncontraceptive reasons, such as menstrual hygiene.

Inform patients of the possible risk for bone loss. Patients and their guardian(s) need to be informed of the potential risk for bone loss, as well as provided information about the substantial evidence of bone recovery and the low risk of osteopenia and the likelihood of recovery, as a routine part of anticipatory guidance in the negotiation surrounding the choice for contraception in the adolescent.

Understand individual risk profile for osteopenia on DMPA. A study by Cromer et al found that the strongest risk factor for osteopenia in an adolescent on DMPA was low body weight, especially a body mass index ≤ 16 [11]. Physical immobility has also been associated with osteopenia: moreover, certain conditions (such as renal disease, cystic fibrosis, anorexia nervosa, previous estrogen deficiency, hyperthyroidism, malabsorption); medications (chronic corticosteroid use and other immunosuppressive drugs, for example); and family history of osteoporosis adversely affect bone density [24]. Therefore, any girl who does not have these risk factors is someone who may reasonably be expected to use DMPA without a predicted occurrence of osteopenia.

It is up to the clinician, in concert with the adolescent and potentially her guardian, to consider the inclusion of bone density monitoring if DMPA is the desired method and some particularly concerning conditions apply to a given patient. Bone densitometry is not routinely indicated either at initiation or follow-up in the apparently healthy adolescent selecting DMPA for contraception. It is also our position that skeletal health concerns should not restrict the duration of DMPA use in most adolescents. However, consideration may be given to obtaining bone density testing in adolescents initiating DMPA if there is concern about particular risk factors for low bone mass as listed above in Item #3. Optimal duration to follow-up DXA testing in these patients has not been determined; however generally, one may retest within two years (not sooner) of the previous DXA assessment.

Issues related to DXA testing. Interpretation of DXA test results can be confusing, especially in this age group. For comparison of results, Z-scores are the correct reference standard for adolescents; a Z-score is the number of standard deviations from a mean value obtained in a healthy group of individuals of similar age. Definition of low bone mass is a Z-score ≥ -2 [25]. The World Health Organization international reference standard for diagnosis of osteoporosis, utilizing T-scores, is not to be used. Important considerations in maximizing the precision of repeat DXA testing is in utilizing the same machine and the same technician, who will ensure the same body positioning. A limitation to application of DXA testing in many clinical settings is the expense. In addition, there is a lack of established criteria in this age group regarding the degree of loss that would provoke clinician concern and action.

Duration of use need not be restricted to two years. The FDA warning states that "Depo-Provera CI should be used as a long-term birth control method (for example, longer than 2 years) only if other birth control methods are inadequate" [2]. Several agencies have interpreted this wording to mean a two-year limit for prescription of DMPA. Given research to date on DMPA-associated bone loss, there is no clear rationale for the choice of such a time limit. In fact, there is evidence that the rate of bone mineral density loss may slow with longer term DMPA use. For example, in three other prospective studies of initiating and/or continuing DMPA users, bone loss slowed after the first one to two years of use [5,6,9].

Recommend 1300 mg calcium carbonate intake plus 400 IU vitamin D and daily exercise to all adolescents receiving DMPA. At present, it has not been established that calcium and vitamin D consumption or physical activity will offset bone mineral density losses related to DMPA use, but these are dietary constituents that provide broad health benefits to this population. The type of exercise that is most effective in increasing bone mineral density in children is that which involves high ground force reaction, i.e., exercise of the weight-bearing variety (e.g., volleyball, racket sports, and running rather than swimming).

Consider estrogen supplementation in those girls with osteopenia (or those who have not had a DXA but are at high risk for osteopenia) who are otherwise doing well on DMPA and have no contraindication to estrogen. As demonstrated in two clinical trials [26,27], estrogen supplementation increases bone mineral density in women on DMPA. The optimal dose, route of administration, and point of maximum benefit to bone have not been established. Generally, menopausal doses have been used, including daily 1 mg oral micronized estradiol, .625 mg conjugated oral equine estrogen, or .05 mg transdermal

estradiol patch concurrent with DMPA treatment. There are insufficient clinical trials to recommend a particular regimen to a targeted user. The use of estrogen has been suggested in those with a demonstrated low bone mass (i.e., >2 standard deviations below the mean of normal values determined for age-matched group), those deemed at high risk based on the risk factors listed above, or in the absence of estrogen contraindications [28–30]. A previous history of recurrent fracture is an important consideration in the management considerations. These decisions must be individualized according to clinician judgment given that DMPA is frequently selected because of contraindications to estrogen use. Moreover, one distinct clinical advantage of DMPA alone is that it obviates the need for daily or weekly compliance for contraceptive efficacy. Adding a second drug would detract from this important attribute.

Need for research. Further research needs include: identifying the magnitude of bone mineral density loss in adolescents who use DMPA for more than two years; further defining of the level of recovery of bone mineral density after discontinuation of DMPA, especially in long-term users and in the very young adolescent; identifying the clinical profile of girls who will most likely experience and sustain bone loss; and determining the possible role of DMPA in changes in bone geometry and related bone strength. Last, research needs to be conducted to develop long-acting hormonal contraception for adolescents that do not carry any risks to the achievement of optimal bone health.

Summary

DMPA, a highly effective contraceptive, is associated with decreases in bone mineral density in adolescents; such decreases are of clinical concern, as bone mass accrual normally is highest during the pubertal years. The clinical concern, however, needs to be placed within the broader context of the high degree of recovery in bone mineral density that has been observed after discontinuation of DMPA, likely low risk of current fracture related to DMPA use, and the physical, social and economic consequences, including possible adverse effects on bone of unintended pregnancy in the adolescent resulting from contraceptive failure. For the majority, the benefits of DMPA outweigh the potential risks. However, patients and families should be informed about the potential for bone loss as part of anticipatory guidance in choosing DMPA and in particular with long-term use. Further research is needed to respond to the many unanswered questions in this field.

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