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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Progestin-Only Contraception and Bone Health

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Abstract
Purpose of Review Progestin-only contraceptive methods are important and effective options for women trying to prevent unintended pregnancy. There is concern about progestin-only methods and bone health, particularly for depot medroxyprogesterone acetate (DMPA), because progestin-only methods can lower estradiol levels through ovarian suppression. This is of particular concern for adolescents building bone and perimenopausal women heading towards menopause.
Recent Findings DMPA does cause temporary bone loss, but this is reversible after discontinuation. Evidence is limited as to whether the decreased bone density and subsequent reversal that is seen with DMPA use leads to an increased risk of fracture in the future. Two observational studies indicate a weak association between DMPA use and fracture risk. Progestin-only implants, pills, and the intrauterine device do not have an impact on bone mineral density or fracture risk.
Summary Use of DMPA or any other progestin-only method should not be restricted due to a theoretical risk of fractures when reproductive-age women face the very real risk of pregnancy.

Keywords Progestin-only contraception · Bone health · Depot medroxyprogesterone acetate · Bone mineral density · Fracture risk

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Introduction

Progestin-only contraceptive methods, including the levonorgestrel intrauterine device (LNG IUD), the etonogestrel implant, depot medroxyprogesterone acetate (DMPA), and progestin-only pills (POPs) are some of the most effective birth control methods available to women. Some women with medical co-morbidities cannot use hormonal methods containing estrogen, so the progestin-only methods are especially important options. Concern about bone health may limit the use of these effective methods. Evidence demonstrates that DMPA does cause reduced bone density, but it also finds that the decreased bone density is reversible after DMPA is stopped. The more important clinical question of whether DMPA use leads to increased fracture risk is a difficult one and has not been conclusively answered with the available evidence. Therefore, use of the progestin-only methods, included DMPA, should not be restricted, even in adolescents and perimenopausal women.

Sex Steroids, Bone Metabolism, and Bone Mineral Density

The female reproductive system plays an important role in skeletal growth and development as well as in the modeling and remodeling of bone throughout the life cycle. Bone is made up of osteoblasts, osteoclasts, minerals (calcium and phosphorus), and an organic matrix of collagen and non-collagen proteins [1]. Bone is metabolically active, continuously undergoing remodeling via osteoclastic (bone resorption) and osteoblastic (bone formation) activity. At menarche, estrogen and other sex hormones stimulate rapid bone mass acquisition and skeletal growth. Estrogen also inhibits bone resorption by suppressing osteoclastic activity [2]. During this

important time of development, bone formation exceeds bone resorption, resulting in bone acquisition. Significant gains in bone mass continue until peak bone density is reached in the third decade of life [3]. At menopause, decreased ovarian function leads to decreased estrogen levels, resulting in rapid bone loss [3]. Estrogen replacement can slow and or prevent this rapid bone loss [4]. The use of hormonal contraception can cause progestational suppression of ovarian estradiol production [5]. This reduction in estradiol levels probably accounts for the decrease in bone mass that has been observed in women treated with some of the hormonal contraceptives [6].

Bone mineral density (BMD) is an important measure of skeletal strength in postmenopausal women. Low BMD, while not the only determinant, is a strong predictor for future fracture risk in postmenopausal women [7]. Other important factors in predicting fracture risk as identified by FRAX, a fracture risk assessment tool developed by the World Health Organization (WHO), include country of residence, ethnicity, age, sex, weight, family history of fracture, personal history of fragility fracture, corticosteroid use, rheumatoid arthritis, smoking, alcohol use, and causes of secondary osteoporosis [8]. Interpreting BMD results in premenopausal women is not as straight forward. Healthy premenopausal women have a lower incidence and prevalence of fractures, and the relationship between BMD and fracture risk is not the same as it is with postmenopausal women [9, 10]. Even in those premenopausal women with low BMD, fracture incidence rates are low [11]. Unlike postmenopausal women, there are no data to support the use of BMD measurements to predict fracture risk in premenopausal women [9].

When looking at the question of bone health and the use of hormonal contraception, the clinically important and relevant question is whether the use of hormonal contraception leads to increased fracture risk. Fracture is a rare outcome and would require following many subjects for many years prospectively. Instead, most studies examining bone health and hormonal contraception use BMD as the surrogate end point for the clinical end of point of interest, fracture risk [12]. Unfortunately, BMD as a surrogate for fracture has not been validated, and, therefore, studies using this surrogate need to be interpreted with caution [12].

DMPA and Bone Mineral Density

Depot medroxyprogesterone acetate is an effective and widely used injectable contraceptive with a typical use failure rate of 6% [13]. DMPA is an appealing option for both adolescents and adults because it offers privacy, efficacy, and non-daily use. Of the progestin-only contraceptives, DMPA has received the most attention regarding the question of bone health because of its higher dose of progestin that causes ovulation suppression but also ovarian estradiol production suppression, resulting in low levels of estradiol [14]. Based on what is known about bone metabolism, DMPA use in adolescence, when bone mass is building, and during perimenopause, when bone mass is expected to decline, has been of particular concern.

A systematic review of progestin-only methods done by WHO and the Centers for Disease Control and Prevention (CDC) found an association between DMPA use and loss of BMD [15]. Cross-sectional and longitudinal studies evaluating BMD in current users of DMPA demonstrate lower BMD in DMPA users versus nonusers [16–22]. Longitudinal studies in adult women have shown a loss in spine and hip BMD of 0.5–3.5% after 1 year of use [17], a loss of 5.7–7.5% after 2 years of use [21, 22], and a loss of 5.2–5.4% after 5 years of use [23]. In adolescents, longitudinal studies report mean decreases in spine BMD ranging from −6.0 to −1.5% at 2 years among DMPA users compared with mean increases of BMD ranging from +5.9 to +9.5% among hormonal contraception non-users [24–28]. A recent study found a dose-response relationship between DMPA exposure and BMD loss in adolescents [29]. A total of 34 subjects were enrolled and randomized to receive a 75-mg, 104-mg, or 150-mg dose of intramuscular DMPA every 12 weeks. At 48 weeks, no significant decreases in BMD were seen in the 75 mg group. The 104 mg group demonstrated a 3.1% significant decrease in the spine BMD from baseline to 48 weeks, and the 150 mg dose group experienced significant decreases from baseline in the spine (4.0%), total hip (3.0%), and femoral neck (4.0%) BMD [29]. Of note, some of the subjects in the 75 mg DMPA group demonstrated medroxyprogesterone acetate levels below the study threshold required for contraceptive efficacy, and one subject had evidence of probable ovulation. It is important emphasize that the 75 mg DMPA dose was used in this study was for research purposes only and should not be considered for contraception. The study investigators concluded that while some individuals may not require doses of DMPA as high as 150 mg to provide contraception and these lower doses may have a beneficial effect on BMD, this must be balanced against the possible risk of decreased contraceptive efficacy [29].

DMPA is associated with loss of BMD during use, but evidence from current cross-sectional and longitudinal studies that include both adult women and adolescents, with a duration of DMPA use of 2 to 5 years and follow-up of up to 5 years suggests that the changes appear to be substantially or fully reversible after DMPA discontinuation, with BMD returning to levels at or near baseline in both adolescents and adults [19, 21, 28, 30, 31•, 32]. Recovery was seen starting as early as 24 weeks after last DMPA injection, and the mean spine BMD of DMPA discontinuers was similar to that of nonusers at 27 to 30 months after last injection [19, 21, 30]. Spine BMD increased more rapidly than hip BMD following discontinuation, with rates of increase ranging from 1.41 to 3.4% per year for spine BMD and from 0.4 to 0.9% per year for hip BMD [19, 21, 30].

In addition to adolescents who are building bone, perimenopausal women are of special interest because they are expected to go through rapid bone loss at the time of menopause. It is important to know whether use of DMPA up until the time of menopause will result in greater bone losses. One study looked at this particular question [33]. The bone mineral densities at the lumbar spine and femoral neck of perimenopausal women aged 45–53 years who used DMPA for at least 5 years and up until menopause were measured annually for 3 years and compared to the BMD of a group of women of similar age who had gone through natural menopause, had never used DMPA, and were not currently using hormonal replacement therapy [33]. The control group of non-users experienced rapid loss of BMD at the spine and hip at 3 years follow-up [33]. The mean change, relative to baseline, at years 1, 2, and 3 was −2.1, −4.5, and −6.1%, respectively, at the lumbar spine ($p < .01$ for all comparisons), and −3.2, −5.4, and −6.1%, respectively, at the femoral neck ($p < .01$ for all comparisons) [33]. In contrast, the DMPA users demonstrated little change in BMD at both sites [33]. The mean change, relative to baseline, at years 1, 2, and 3 was −2.3, −1.6, and −0.3%, respectively, at the lumbar spine and +0.4, +1.2, and +0.8%, respectively, at the femoral neck [33]. The bone density loss at the lumbar spine at year 1 was statistically significant ($p = .03$); all other BMD comparisons for the DMPA-users were non-significant [33]. At the time of menopause there is a hormone-mediated loss of BMD that occurs, and the authors postulated that women using DMPA up until menopause had already experienced this hormone-mediated (hypoestrogen) loss and did not undergo additional BMD loss when they went through menopause [33]. Several additional studies compared the BMD of postmenopausal former DMPA users to never users and found the BMD to be similar between groups, providing additional evidence for the short term and reversible changes associated with DMPA use [34–36].

Etonogestrel Implant, Progestin-Only Pill, and the Levonorgestrel Intrauterine Device and Bone Mineral Density

The etonogestrel (ETG) contraceptive implant is effective for at least 3 years and is one of the most effective methods available, with a typical use failure rate of 0.05% [13]. Women of all ages choose the ETG implant because its ease of use and high efficacy. ETG implants inhibit ovulation, but estradiol levels remain close to the levels found in the normal early follicular phase [37, 38].

The evidence regarding ETG use and bone health is more limited, and results are somewhat mixed but overall reassuring. Several studies comparing the BMD of ETG implant users to non-hormonal method users found no difference in BMD at 12 and 24 months of implant use [38, 39]. A third prospective but uncontrolled study measured BMD at baseline and again at 18 months after implant insertion, and found a lower BMD at the midshaft ulna but no difference in BMD at the distal radius [40]. Lastly, a cross-sectional study compared users of the ETG implant for at least 2 years to users of non-hormonal contraception. A significant difference in BMD was found in ETG users compared to nonhormonal users at the distal radius and ulna but no BMD difference at the spine and femur [41].

Progestin-only pills (POPs) contain a low dose of hormone and prevent pregnancy through thickening of the cervical mucus and not through suppression of ovulation. Estradiol levels remain normal and unaffected, and POPs have no known negative effect on BMD [42, 43].

The levonorgestrel-releasing intrauterine device (LNG IUD) provides intrauterine low dose hormone and prevents pregnancy primarily through thickened cervical mucus. Estradiol levels remain normal during LNG IUD use [44]. Both cross-sectional and longitudinal studies demonstrate that the short and long-term (up to 7 years) use of the LNG IUD has no adverse effect on BMD as compared to users of the non-hormonal IUD [45–47].

DMPA and Bone Fractures

Fragility fractures are rare in premenopausal women. DMPA does cause a decrease in bone mass, but whether this leads to an increase in fracture risk is the clinically important question. This question is difficult to answer with a randomized controlled trial due to the rarity of fractures in the population of reproductive-aged women. Fracture is not usually an outcome in studies of premenopausal bone health [48]. Observational studies attempt to answer this important clinical question. A recent systematic review looked at the evidence from these observational studies on steroidal contraceptives and bone fractures in women [49•]. Two DMPA studies using large databases reported increased fracture risk for longer current use of DMPA [50, 51]. These studies also noted an increased fracture risk in women if they had ever used DMPA in the past. A cohort study of DMPA users versus users of other types of hormonal contraceptives (mostly oral contraceptives) found that DMPA users had an increased fracture risk at any skeletal site compared to users of other hormonal contraceptives (the crude incidence rate ratio for DMPA users versus non-users 1.41, 95% CI 1.35–1.47) [52]. However, further analysis of the cohort before any contraception was started found that the crude incidence rate ratio for fractures for women who would later become DMPA users was 1.28 (95% CI 1.07–1.53) compared with women who never used DMPA, indicating that the risk of fractures did not increase after starting DMPA but was present before DMPA was initiated, and that women who choose DMPA may be at higher risk for

fracture before starting DMPA [52]. The investigators of this study also looked more closely at the site of fracture, breaking fracture site down into three groups: axial (vertebrae, hip, and pelvis), appendicular skeleton (arm, leg, wrist, ankle, hand, foot, clavicle, rib or sternum, and shoulder), and all other fractures (e.g., finger, toe, skull, face, multiple trauma, and unspecified) [52]. Hip and vertebral (axial) fractures are more sensitive to BMD changes and are routinely used as endpoints in osteoporosis trials [52]. Fractures of the finger, toe, face, and skull are more likely to result from trauma [52]. Compared with non-use, DMPA users had more fractures that fell into the appendicular and all other fractures categories, but had no excess risk for axial site fractures (incidence rate ratio 0.95, 95% CI 0.74–1.23) [52]. In one cohort study following BMD over time in DMPA users versus users of non-hormonal contraceptive methods, fractures were recorded as adverse events, and there was no difference in fractures between the study groups [23]. The most recent study published looking at the impact of DMPA on fracture risk, and not included in the previous systematic review, identified women with a first-time fracture diagnosis and matched them with controls matched for age and sex from a large database. Investigators found a slightly higher use of DMPA in fracture cases versus controls (11 versus 7.7%). The relative risk of fracture was adjusted for body mass index, smoking, asthma, epilepsy, use of other progestins, beta-blockers proton pump inhibitors, systemic corticosteroids, benzodiazepines, serotonin reuptake inhibitors, anticonvulsants, and contraceptives not under investigation. The adjusted OR for developing a fracture in patients with current use of DMPA compared to non-use was 0.97 (95% CI 0.51–1.860, 2.41 (95% CI 1.42–4.08), and 1.46 (95% CI 0.96–2.23) for 1–2, 3–9, and ≥10 prescriptions, respectively. The adjusted OR for developing a fracture in patients with past use of DMPA compared to non-use was 0.96 (95% CI 0.73–1.26), 1.14 (95% CI 0.86–1.51), and 1.55 (95% CI 1.07–2.27) for 1–2, 3–9, and ≥10 prescriptions, respectively [53].

Because of the low dose of levonorgestrel, LNG IUD use does not have systemic effects and does not result in suppression of ovarian estradiol production, so an adverse effect on fracture risk is not expected. Vestergaard et al., looked at LNG IUD use and fracture risk and found that ever use of the LNG IUD versus non-use resulted in decreased fracture risk (adjusted OR 0.75, 95% CI 0.64–0.87) and fracture was less likely for those who used the LNG IUD for 1.6 to 4 years) (adjusted OR 0.77, 95% CI 0.59–0.99) [54]. The authors postulate a non-pharmacological effect for the reason LNG IUD use results in decreased fracture risk. They suggest that this decrease in fracture risk is related to lifestyle characteristics, such as IUD users living in more stable relationships or being less "risk takers" than women using other types of contraception [54]. There are no studies looking at fracture risk with the use of the ETG implant or POPs.

The Black Box Warning, Patient Counseling, and Management

In November 2004, the U.S. Federal Drug Administration (FDA) placed a black box warning in DMPA package labeling cautioning providers that long-term use of the drug may result in loss of BMD and that this loss may not be completely reversible with cessation of DMPA [55]. 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 fractures in later life and states that DMPA should only be used as a long-term method (longer than 2 years) if other birth control methods are "inadequate" [55]. The FDA warning was based on the findings from a small sample size of less than 50 adolescents [31•].

When counseling women and adolescents about birth control options, providers need to assess the appropriate of use of all of the different methods based on patient characteristics, including when considering DMPA use. If DMPA is being considered, providers should talk to patients about the benefits and risks of DMPA and should discuss the FDA black box warning and the effects on bone density and possible effects on fracture risk. However, these concerns about bone health should not prevent providers from prescribing DMPA or continuing DMPA use beyond 2 years in women or adolescents [31•]. Certain co-existing medical conditions may influence counseling and recommendations for hormonal contraceptive use, including DMPA use, and counseling should be individualized. Providers should recommend regular weight-bearing exercise, smoking cessation, and age-appropriate calcium and Vitamin D intake to all patients. While there are no studies demonstrating that these healthy measures will decrease or prevent BMD loss during DMPA use, these recommendations can have overall health benefits [31•].

Estrogen replacement is not recommended for DMPA users. While estrogen replacement has been shown to improve bone density in DMPA users, estrogen replacement carries risk, and it is not known whether estrogen replacement prevents fractures [31•, 56, 57]. Routine BMD monitoring with dual-energy x-ray absorptiometry (DXA) is not recommended in DMPA users because DXA has not been validated in reproductive-age women and adolescents [31•].

Conclusions

The risk of unintended pregnancy is real and it carries substantial personal and public health consequences. The use of reliable hormonal contraception can decrease the risk of unintended pregnancy. Progestin-only contraceptive methods are some of the most effective options available and for some women with medical comorbidities, the only safe hormonal methods. Evidence demonstrates that some progestin-only

methods do cause loss of bone density, but that it appears that this loss is temporary and reversible in both adolescents and adults. BMD should not be used to predict fracture risk in premenopausal women. The more important clinical question is whether use of progestin-only methods leads to increased fracture risk and this question has not definitively been answered by the available evidence. Limited evidence shows a weak association of DMPA use with fracture. Major health organizations, such as WHO and American Congress of Obstetricians and Gynecologists (ACOG) have not recommended restricting DMPA use among women aged 18 to 45 years [58, 59•]. In the CDC Medical Eligibility Criteria for Contraceptive Use, DMPA is category 1 (no restriction for use) for women aged 18 to 45 years. For women less than 18 and greater than 45 years of age, DMPA is category 2, which indicates the advantages of using the method outweigh any theoretical or proven risks. Ultimately, the reality of using less effective birth control methods and the subsequent increase in pregnancy risk must be balanced with the theoretical risk of increased bone fractures.

Compliance with Ethical Standards

Conflict of Interest Michelle M. Isley declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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