FACULTY OF FAMILY PLANNING AND REPRODUCTIVE HEALTH CARE
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REVIEW

This review is intended as an educational exercise and reports the personal views of the authors

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Depo-Provera® and bone density

Babatunde A Gbolade, MRCOG, MFFP, MSc, MPhil, FRCPI, *Consultant Gynaecologist and Director of Fertility Control Unit, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK*

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Introduction

Depo-Provera® (depot medroxyprogesterone acetate, DMPA) is the most widely used injectable method of contraception, which is effective, reversible, does not have a deleterious effect on lactation and does not interfere with sexual activity. Each millilitre is composed of microcrystals of 150 mg medroxyprogesterone acetate Ph Eur suspended in an aqueous solution.[1] It is given every 12 weeks by deep intramuscular injection into the gluteal muscle. (The deltoid is used in communities where exposure of the gluteal region is not culturally acceptable.) When administered in this dose, studies have shown failure rates ranging from 0 to 0.7 pregnancies per 100 women years.[1] However, despite its efficacy and acceptability, concern is increasingly being expressed about its potential deleterious effect on bone mineral density (BMD). This concern has resulted in clinicians becoming reluctant to recommend this method for long-term contraception. This FACT reviews current and emerging data pertaining to this issue.

Mechanism of action

A dose of 150 mg of Depo-Provera® effectively suppresses ovulation and ovarian production of oestradiol, by inhibiting the secretion of pituitary gonadotrophins. It alters the yield, composition and physical characteristics of cervical mucus and induces the formation of a thin and quiescent-type endometrium with decreased glandular activity. Following prolonged use, the endometrium becomes atrophic and most women become amenorrhoeic. Amenorrhoea occurred in 8% of women after their first injection and in 45% during the first 12 months of use.[2]

Depo-Provera® and serum oestradiol levels

Depo-Provera® abolishes peak or ovulatory levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH) but normal basal levels of these hormones are maintained throughout treatment.[3] Goldzieher et al. found that the range of FSH and LH levels in women using Depo-Provera® for up to 2 years and in non-users were the

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same; a finding suggesting that the hypothalamic–pituitary axis is not completely suppressed by long-term use of Depo-Provera®.[4] Cross-sectional studies show that serum oestradiol levels range from 15 to 318 pmol/l.[3,5–7] In nearly all women, after up to 5 years of Depo-Provera® use, serum oestradiol levels remain above those found in postmenopausal women. Serum levels of oestradiol are maintained in the range found in the early follicular phase of women with ovulatory cycles. Consequently, women using Depo-Provera® generally do not have symptoms or signs of oestrogen deficiency.

BMD and osteoporosis

The skeleton is composed of 80% compact or cortical bone and 20% trabecular bone. Cortical bone forms the outer surface of all bones, while trabecular bone forms the greater part of each vertebral body and the epiphyses of the long bones and is present in other sites such as the iliac crest. Bone mass is a major determinant of skeletal strength although the internal architecture is also of importance. There is wide variation in bone mass both between and within races; Caucasians generally have lower bone mass than black people while Asians have yet lower bone mass. Attainment of peak bone mass is determined by genetic potential, with nutrition, exercise, hormonal status and disease acting as modifying influences.[8]

However, available evidence indicates that oestrogens are of crucial importance in attainment of peak bone mass in women.[9–14] Throughout adult life, bone formation and resorption are closely coupled so that for there to be a net loss of bone, there must be a partial breakdown of the co-ordinated activity of osteoblasts and osteoclasts.[8] Osteoclast activity (bone resorption) is down-regulated by oestrogens and in hypo-oestrogenic states, bone resorption exceeds bone formation. Bone mass accumulates rapidly during the first two decades of life, with a spurt in the adolescent years, followed by a period of consolidation, reaching its peak in the third decade of life.[15] Bone mass at any particular age after skeletal maturity is dependent on the peak bone mass attained at skeletal maturity and the subsequent loss. The level at which bone mass peaks is an important predictor of the risk of osteoporosis in later life,[16] as the process of bone loss begins slowly during the pre-menopause years.[17] Osteoporosis is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.[18] BMD is defined as the bone mineral content divided by the area scanned and is the best measure for comparing serial scans and follow-up. For comparative purposes, categories of osteoporosis are defined in terms of bone mineral density and fractures (Table 1).[19]

Table 1 *Categories of osteoporosis*

Established osteoporosis Bone mineral density (BMD) more than 2.5 SD below the mean value of peak bone mass in young normal women, and the presence of fractures.
Osteoporosis BMD more than 2.5 SD below the mean value of peak bone mass in young normal women.
Osteopenia (or low bone mass) BMD between minus 1 SD and minus 2.5 SD of the mean value of peak bone mass in young normal women.
Normal BMD not more than 1 SD below the mean value of peak bone mass in young normal women.

These values for BMD apply only to Caucasian women and their relevance in other ethnic groups and men is unknown.[20] There is an increasing gradient of risk of fracture with decreasing bone density; a decrease in bone density of one standard deviation (1 SD) being associated with a 1.5–3.0-fold increase in fracture risk.[21–24] Reduced bone mass correlates well with fracture risk and is one of the best predictors, especially if measured at the future site of potential fracture such as the femoral neck or spinal vertebrae.[17,25,26] However, the correlation is not sufficient to allow for an accurate prediction of which individual may suffer a fracture in the future. There is an overlap between bone mass values at which fractures will and will not occur and it is not presently possible to define an absolute cut-off point.

Dual-energy x-ray absorptiometry (DEXA) is widely used for measuring bone density and assessing fracture risk because of its non-invasive nature, relatively low radiation exposure rate, reproducibility and greater measurement precision.[27] The BMD is recorded as grams per centimetre squared (g/cm^2) and expressed as T and Z scores. The T score is the number of SD above or below the mean reference value for young healthy adults, while the Z score is the number of SD above or below the mean reference value of a healthy population matched for age and sex. Using these scores, the World Health Organization (WHO) defines osteopenia as a T score of minus 1 to minus 2.5 and osteoporosis as below minus 2.5.[19]

Depo-Provera® and BMD

Because Depo-Provera® causes ovarian suppression and consequently, in some women, low oestrogen levels, concern has been growing about bone loss in long-term users. However, there are no published studies showing a linear relationship between oestradiol levels and BMD in these patients; in fact, two studies showed that there was no significant correlation between bone density and serum oestradiol level.[6,7] Several studies have sought to ascertain the effects of long-term use of Depo-Provera® on bone density but the results have been mixed. This is not surprising given the fact that most of the studies have been cross-sectional in design, of short duration, and have used different measuring techniques at different sites in different population groups with small numbers. Cross-sectional studies from New Zealand have shown bone loss in the hip and spine.[28–30] However, the lost spinal bone density was restored in a small subgroup of the original study group, within 2 years following discontinuation of long-term use of Depo-Provera®.[30] They also found that women who started using Depo-Provera® after the age of 20 years and who had used it for 15 years or less had a significantly higher bone density than the remainder of their cohort of study participants.[29] The same group found that oral medroxyprogesterone acetate (MPA) at a dose of 50 mg daily in 13 premenopausal women reduced bone density in the spine compared to 12 controls.[31] Femoral neck bone density measurements did not differ between the groups. On cessation of therapy, spinal bone density showed significant recovery. They therefore concluded that, when given in doses sufficient to induce hypogonadism, MPA use is associated with significant early loss of trabecular bone.

A Brazilian cross-sectional study measured BMD at the mid-shaft and at the distal radius of the non-dominant forearm using single-photon x-ray absorptiometry in 50 premenopausal women who had used Depo-Provera® for at least 1 year and 50 women who had never used hormonal contraceptive methods. It found decreased bone density at

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the mid-shaft and the distal portions of the forearm in Depo-Provera® users. However, the difference in the mid-shaft was not statistically significant and the decrease in both sites was not related to the duration of Depo-Provera® use.[32] Another Brazilian cross-sectional study performed DEXA measurements on 72 women who had used Depo-Provera® for at least 1 year and on 62 non-users. It found that bone density was significantly lower for Depo-Provera® users than for controls in the lumbar spine, femoral neck, Ward's triangle and trochanter. [NB. Five groups of normal trabecular bone course through the proximal femur. Ward's triangle lies in the gap between the superior arcuate and the cortical medial primary trabeculae. It enlarges in the osteoporotic femoral neck.] The decrease in spinal bone density was associated with lower body mass index (BMI) and duration of amenorrhoea, while older age, lower BMI and longer duration of amenorrhoea were associated with lower bone density in the femoral neck.[33]

A cross-sectional study from the UK which looked at women who had used Depo-Provera® for 1–16 years, most of whom were amenorrhoeic and biochemically hypo-oestrogenic, found insignificant decrease in bone density measurements relative to the normal population mean.[6] Data from a cross-sectional study in Hong Kong showed that long-term use of Depo-Provera® was associated with significantly lower bone density in the lumbar vertebrae, neck of femur, and Ward's triangle and that the decrease in the lumbar vertebrae was more pronounced with age.[34] However, the results of a longitudinal study over a 3-year period by the same group failed to meet the projected bone loss derived from the previous cross-sectional study. It confirmed the findings of others that the duration of Depo-Provera® use is not significantly correlated with the rate of bone loss. This led to the suggestion that the rate of bone loss is probably non-linear, with a rapid loss in the first 5 years and a levelling off afterwards.[35]

The WHO multicentre cross-sectional study involving seven centres in three regions of the developing world looked at 2474 women aged 30–34 years old who had used Depo-Provera®, oral contraceptives or levonorgestrel implants for at least 24 months compared with non-use or less than 6 months use of hormonal contraceptives. BMD was measured at the distal radius and the mid-shaft of the ulna using single-photon x-ray absorptiometry. For all three hormonal methods, the magnitude of changes in bone density was small and less than 1 SD from the mean of those who had never used hormonal contraceptives.[36]

Other studies of long-term use of Depo-Provera® have found a neutral effect on bone density. The study by Virutamasen et al. looked at bone density in the femoral neck of Depo-Provera® users and non-users, using plain x-ray of trabecular bone patterns graded according to the Singh index. The investigators found that the bone density in Depo-Provera® users was not statistically different from that in controls.[37] While there is an increased risk of fracture of the proximal femur in patients with a Singh index of grade 3 or less, many patients with fractures have normal values.[38] As result, the findings of this study are of limited value. [NB. The Singh index assesses loss of bone mass and changes in the trabecular pattern in the proximal femur. There are six grades with the lower numbers representing low bone mass.[39]]

Taneepanichskul et al., in a cross-sectional study, examined the effect of long-term use of Depo-Provera® compared with use of intrauterine devices (IUDs) on bone density of the non-dominant distal and ultradistal forearm.[40] [The distal forearm measurement corresponded to 24 mm of radius and ulna proximal to the site where the distance between radius and ulna is 8 mm. This site contains approximately 25% trabecular bone and 75% cortical bone. The ultradistal forearm measurement corresponds to a 15-mm strip of radius distal to the point where the gap between the radius and ulna is 8 mm. This site contains approximately 65% trabecular bone and 35% cortical bone.[41] In this study, the distal forearm was taken as cortical bone and the ultradistal forearm as trabecular bone.]

No differences in mean BMD between Depo-Provera® and IUD users was demonstrated. However, as expected, serum oestradiol levels were significantly lower in Depo-Provera® users than in the comparators. The same workers found no differences in bone mass in Depo-Provera® users as compared with Norplant® implant users.[42] A small prospective, randomised study from Sweden, which investigated the differential effects of Depo-Provera® and implants on bone density in the distal forearm, found stable values in Depo-Provera® users at 6 months.[43]

Of greater concern is the effect of long-term use of Depo-Provera® on bone density of adolescents. As indicated earlier, bone mass accumulates rapidly during adolescence,[15] and most of the bone mass in the spine and hip is accumulated by the age of 18 years.[44] Since attainment of peak bone density appears to be the single most useful measure to prevent osteoporosis and fractures in later life, it would seem prudent to avoid any drugs that would prevent attainment of peak bone density during adolescence. There is a paucity of data about the effect of long-term use of Depo-Provera® on bone density in adolescents but three studies have recently addressed this issue.

Scholes et al. undertook a cross-sectional comparison of bone density levels in women using Depo-Provera® and in non-users. Overall, age-adjusted mean bone density levels were lower for Depo-Provera® users than for non-users at all anatomic sites measured. Even after multivariate adjustment for other risk factors, the differences continued to be significant and the major differences in bone density between users and non-users occurred in the group of women aged 18–21 years. A significant dose–response relationship was noted between longer use of DMPA and decreased bone density levels in this age group.[45]

Cromer et al., in their longitudinal study, examined bone density among adolescents receiving different forms of hormonal contraception together with that of control subjects.[46] Baseline and 1-year measurements of lumbar vertebral bone density were obtained in girls aged 12–21 years receiving depot medroxyprogesterone acetate (n = 15), levonorgestrel (Norplant®) (n = 7) or oral contraceptives (n = 9) and in girls receiving no hormonal treatment (n = 17). After 1 year, bone density decreased 1.5% in Depo-Provera® users, compared with increases of 2.5% in Norplant® users, 1.5% in oral contraceptive users, and 2.9% in control subjects. In a sub-sample of Depo-Provera® users (n = 8), Norplant® users (n = 3) and control subjects (n = 4), bone density measurements were repeated after 2 years. Bone density increased a total of 9.3% in Norplant® users and 9.5% in control subjects but decreased a total of 3.1% in Depo-Provera® users. This study had a high dropout rate and incomplete follow up. However, the data suggested that Depo-Provera® might suppress, at least temporarily, the expected skeletal bone mineralisation in adolescents, whereas Norplant® and oral contraceptives are associated with the expected increase in bone density in this population.

One small prospective controlled study (cited in *The Contraception Report*)[47] showed that mean spinal bone

density was 10% lower in DMPA users compared with controls, 12–18 months after baseline measurements were taken. The study was conducted on 14 adolescents (mean age 17 years). Bone density loss at the femoral neck was not significant but the degree of spinal bone density loss correlated with the commencement of DMPA use in relation to the menarche. The negative impact on bone density in those who started Depo-Provera® within 3 years of menarche was greater that in those who started later. Larger studies in adolescents are needed to confirm these findings.

Conclusions

At the present time, a definite evidence-based answer to the concern of the adverse effect of long-term use of Depo-Provera® on bone density is not possible because of the conflicting data from the various studies. Some of the discrepancy between the data obtained by the different studies is related to differences in the anatomical sites of measurement of bone density; reductions in bone mass being less pronounced in the forearm than in the lumbar vertebrae.[33] The loss of bone density in long-term users of Depo-Provera® appears to be a transient and reversible phenomenon similar to what occurs during lactation.[48] Just as bone density loss is reversed following cessation of lactation,[49] discontinuation of Depo-Provera® results in reversal of bone loss.[30] Furthermore, data from a study of bone density in postmenopausal former Depo-Provera® users in New Zealand showed that their bone density was similar to that of women who had never used Depo-Provera®,[50] a rather reassuring finding. While it can be recommended that concerns about the reversible loss of bone density should not be a contraindication for using Depo-Provera®, caution needs to be exercised in the case of those with risk factors for low bone density such as amenorrhoeic athletes, cigarette smokers, women with anorexia nervosa, perimenopausal women and those on long-term treatment with corticosteroids.

Recommendations

A definitive evidence-based guideline for management of patients on long-term use of Depo-Provera® concerned about bone mass loss is not possible at the present time. This is due to the conflicting results of the relevant studies, the amount of bone mass loss, similarity to the transient hypo-oestrogenism of lactation and evidence of some recovery of bone mass following cessation of use. Until solid evidence becomes available, what follows below seems a reasonable approach.

Every female contemplating use of Depo-Provera® should be informed of the association of long-term use with loss of bone mass.

Lifestyle measures that are concerned with building and maintaining a skeletal mass such as diet, exercise, alcohol and smoking should be discussed and those with adverse risk factors discouraged.

Patients on long-term, high-dose corticosteroid therapy should be discouraged from using Depo-Provera®.

There is no need for routine measurement of serum oestradiol since by its very mode of action, low serum levels are the norm. If there is concern about osteopenia and risk of fracture after some years of use (especially in the presence of symptoms, heavy smoking, etc), the bone density should be checked. However, the threshold for triggering this expensive investigation remains undetermined.

In the author's view, administration of exogenous oestrogen is neither evidence-based, nor warranted and may actually affect and complicate compliance.

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Discussion points

1. **Do we need to routinely measure serum oestradiol levels in long-term users of Depo-Provera® in order to assess risk of osteopenia?** In nearly all women, after up to 5 years of Depo-Provera® use, serum oestradiol levels remain above those found in postmenopausal women and serum levels of oestradiol are maintained in the range found in the early follicular phase of women with ovulatory cycles. Besides, there are no published studies showing a linear relationship between oestradiol levels and BMD in these patients. One cross-sectional study[6] and a prospective longitudinal study[7] did show that there was no significant correlation between bone density and serum oestradiol levels.
2. **Does the degree of bone loss in long-term users of Depo-Provera® put them at risk of osteoporosis?** Most of the data from the different studies show bone density measurements within 1 SD of the mean value of peak bone mass in young normal women, and therefore not at a level for intervention according to WHO criteria.[19]
3. **Do adolescents who use Depo-Provera® recover lost bone after discontinuing it and if not should they be given 'add-back' oestrogen during long-term use?** For women under 18 years of age, there are theoretical concerns regarding the hypo-oestrogenic effect particularly due to DMPA use. The WHO medical eligibility criteria consider Depo-Provera® to be generally acceptable for women aged 18 years or younger, because the proven benefits of using the method outweigh the theoretical risk (Category 2).[51] However, data from available studies do not provide any indication of the extent of recovery of lost bone in adolescents following discontinuation of Depo-Provera®. Although some prescribe it, there is no evidence that 'add-back' oestrogen given during long-term use might reduce the amount of bone loss or at what point to commence the treatment. A pragmatic approach might be to avoid use of Depo-Provera® under the age of 16 years until evidence to the contrary becomes available.
4. **Do former long-term Depo-Provera® users have lower bone density at the menopause and therefore a greater risk of osteoporosis and fractures?** There is concern that there may be residual osteopenia in former users such that their postmenopausal fracture risk is increased. Only one study has addressed this issue and the results are reassuring. Overall, there were no significant differences in bone density at any site between the women who had previously used Depo-Provera® and never-users. There was no correlation between bone densities and the duration of Depo-Provera® use, the age at discontinuation of Depo-Provera®, or the time between Depo-Provera® discontinuation and the menopause. It was therefore concluded that any residual effects of Depo-Provera® use on postmenopausal bone density are small and therefore unlikely to have a substantial impact on fracture risk in the postmenopausal years.

F A C T **Faculty Aid to CPD Topics**

A **CPD** Self-Assessment Test

QUESTION SHEET

Review No. 2002/01

To be reviewed not later than 31st March 2007

Depo-Provera® and bone density

Indicate your answer by ticking the appropriate box for each question

		True	*False*
1.	All hormonal contraceptives suppress ovarian production of oestrogen to some degree.	☐	☐
2.	Depo-Provera® works mainly by suppression of ovulation.	☐	☐
3.	Most of the bone mass in the hip and vertebral bodies is accumulated in young women by 18 years of age.	☐	☐
4.	All studies of long-term users of Depo-Provera® have shown significant loss of bone mass compared to non-users.	☐	☐
5.	Some studies have shown bone mass loss of up to 25% following long-term use of Depo-Provera®.	☐	☐
6.	Women have a higher bone mass than do men at all ages, with a rapid loss at the expected age of menopause.	☐	☐
7.	Bone mass loss following long-term use of Depo-Provera® does not persist after the menopause.	☐	☐
8.	Serum oestradiol level is the best predictor of risk of future fracture and should be measured routinely in users of Depo-Provera®.	☐	☐
9.	Since low bone density at various sites is predictive of fracture for groups of women, it can identify individuals who will fracture.	☐	☐
10.	After using Depo-Provera® for 5 years, all women should have their serum oestradiol and bone density measured.	☐	☐

Turn to page 50 for answers

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