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Bone loss associated with long-term use of depot medroxyprogesterone acetate

與長期使用長效安宮黃體酮有關的骨質流失

On 17 November 2004, the United States Food and Drug Administration issued a black box warning on the long-term use of depot medroxyprogesterone acetate stating that bone loss might be irreversible with use of more than 2 years. Despite the seriousness of such a safety warning, the Food and Drug Administration provided no clinical recommendations. Various professional bodies have made different recommendations on the management of women prescribing such long-term injections but there is no consensus on the best practice. Thus individual institutions need to revise service protocols. The Health Services Subcommittee of the Family Planning Association of Hong Kong has reviewed the scientific evidence from international and local studies and made its recommendations in a meeting held on 1 March 2005. This article aimed to share our opinion with other medical professionals in Hong Kong.

美國食物及藥物管理局在 2004 年 11 月 17 日，對長期使用長效安宮黃體酮發出黑盒警告，表示若使用超過兩年，骨質流失情況會無法逆轉。雖然有關的警告非常嚴重，當局並未有提出任何的臨床建議。不同的專業團體就如何處理那些長期注射此藥物的女性提出了不同的建議，但如何獲得最佳效果仍未有一致意見，令個別機構需要修改其治療方案。香港家庭計劃指導會的醫療服務小組委員會在檢討過國際和本地的科研資料後，於 2005 年 3 月 1 日的會議中提出其臨床建議。本文旨在與其他醫療專業人士分享我們的意見。

Key words:
Bone demineralization;
Contraceptive agents, female;
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關鍵詞：
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Introduction

The United States Food and Drug Administration (FDA) announced on 17 November 2004 that a black box warning would be added to the labelling of depot medroxyprogesterone acetate (DMPA).[1] It emphasised that "prolonged use of DMPA may result in significant loss of bone density, and that the loss is greater the longer the drug is administered. This bone density loss may not be completely reversible after discontinuation of the drug. Therefore a woman should only use DMPA as a long-term birth control method (for example, longer than 2 years) if other birth control methods are inadequate for her."

The addition of the black box warning is a result of the drug manufacturer's (Pfizer) analysis of post-marketing research data that has not been peer reviewed.[2] A black box warning of the FDA is the harshest label warning used to highlight special problems, especially those that have serious implications. It also provides health care professionals a clear understanding of a potential medical complication or serious side-effect so that a prudent decision can be made to maximise the

Table. Summary of international responses

Organisation*	Responses
PPFA	Limit use to no more than 2 years unless no better alternatives Adequate calcium intake and exercise
UK CSM	In adolescents, use DMPA† as first line if no better alternatives Users of all age, re-evaluate after use for more than 2 years Change method if woman is at risk of osteoporosis
UK FFPRHC	Adopt CSM recommendations Only history taking and lifestyle assessment are needed at the re-evaluation No need for bone density measurement at re-evaluation
Health Canada	Adopt recommendations by the pharmaceutical company No additional recommendations
CMA	Consider other risk factors for osteoporosis when deciding on the use of DMPA Prolonged use acceptable only if no better alternative contraceptives are available Bone mineral density should be monitored in women who have used it for more than 2 years Advise calcium, exercise, and smoking cessation
WHO and IPPF	Continue to adopt the latest recommendations of the Medical Eligibility Criteria for Contraceptive Use[8]: • Women aged <18 and >45 years, DMPA use is in category 2 (benefits generally outweigh theoretical or proven risk) • All other women are in category 1 (no restriction for use)

* PPFA denotes Planned Parenthood Federation of America, UK CSM United Kingdom Committee on Safety of Medicines, UK FFPRHC United Kingdom Faculty of Family Planning and Reproductive Health Care, CMA Canadian Medical Association, WHO World Health Organization, and IPPF International Planned Parenthood Federation

† DMPA denotes depot medroxyprogesterone acetate

benefits and minimise the risks associated with the use of a drug.

In this case, two main groups of women are affected: (1) women who have used DMPA for more than 2 years and prefer to continue; and (2) adolescents and women in early adulthood who are at a critical stage of bone accretion.

International responses

In November 2004, the Planned Parenthood Federation of America advised women to limit DMPA use to no more than 2 years unless alternatives were unacceptable and ensuring adequate calcium intake and exercise.[3] No comment was made on whether bone mineral density assessment was required (Table).[3]

The Chairman of the United Kingdom Committee on Safety of Medicines (CSM) wrote to health care providers and advised that: (1) in adolescents, DMPA may be used as first-line contraception only after other methods have been discussed with the patient and considered to be unsuitable or unacceptable; (2) in women of all ages, careful re-evaluation should be carried out in those who wish to continue use for more than 2 years; (3) in women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered.[4]

The United Kingdom Faculty of Family Planning and Reproductive Health Care issued a statement[5] in November 2004 stating that the CSM's recommendation should be adopted. It also recommended that only history taking and lifestyle assessment were needed and there was no need for bone density measurement.

Health Canada endorsed the Safety Information from Pfizer Canada in November 2004 but did not make additional recommendations.[6] In March 2005, the Canadian Medical Association recommended patient's risk factors for osteoporosis be included in the risk-benefit analysis when prescribing DMPA and the drug should be used for more than 2 years only if other methods of birth control are inappropriate. Women who use the drug for more than 2 years should have their bone density monitored. Lifestyle modification such as calcium and vitamin D intake, exercise, and smoking cessation are also advisable.[7]

When the World Health Organization (WHO) published the Medical Eligibility Criteria for Contraceptive Use in 2004,[8] it had already considered the effect of DMPA on bone in women of various ages. The use of DMPA in women aged younger than 18 years and older than 45 years was assigned category 2 status (ie benefits generally outweigh theoretical or proven risk). The use in women between 18 and 45 years was assigned category 1 status (ie no restriction for use). The WHO expert group has recently convened a scientific review of injectable progestin contracep-

Box. Summary of scientific evidence

Adverse effect of DMPA* on bone density
Cross-sectional[11-17,30,33,34]
Longitudinal[22,23,31,35,36]
No bone loss while on DMPA
Cross-sectional[18-21,32]
Bone loss reversible after cessation of DMPA[16,22,24,36]
Osteoporotic fractures associated with DMPA use†

* DMPA denotes depot medroxyprogesterone acetate
† No evidence

tives (such as DMPA) and reduced bone density on 21-22 June 2005 and recommended that[9]:

(1) There should be no restriction on the use of DMPA, including no restriction on duration of use, among women aged 18 to 45 years who are otherwise eligible to use the method.
(2) Among adolescents (menarche to <18 years) and women over 45 years, the advantages of using DMPA generally outweigh the theoretical safety concerns regarding fracture risk. Since data are insufficient 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 user.

The International Planned Parenthood Federation (IPPF) has adopted the WHO eligibility criteria. No specific action related to bone mass preservation was mentioned in its Service Delivery Guideline, and history taking or lifestyle assessment before the prescription of DMPA or at annual assessment was not suggested.[10] The IPPF has not responded to the FDA warning so far (http://www.ippf.org).

The scientific evidence

Cundy et al[11] first reported the adverse effect of DMPA on bone mass attainment and retention. Following this report, many cross-sectional studies were performed to evaluate bone mineral density in DMPA users. Some studies found lower bone mineral density[12-17] while others found no bone loss.[18-21] None have documented any clinical consequences (ie osteoporotic fractures) associated with the bone loss. Thus there is a possible but unproven fracture risk posed by the modest bone loss. Longitudinal studies with follow-up that vary from 1 to 3 years have shown that DMPA use is associated with reduced bone density (Box).[22,23]

Some studies examined the reversibility of bone loss after cessation of DMPA use and concluded that such loss is largely reversible.[16,22,24] One study showed that bone loss in DMPA users during menopause transition was slower than in non-users.[25] It was also observed in another small study that a history of DMPA use was unlikely to have a substantial impact on fracture risk in post-menopausal women.[26] Thus the clinical risk of long-term DMPA use appears to be low, if any exists at all.

Bone loss is a natural part of ageing. Bone mass begins to increase at the time of menarche[27] and continues to rise until the late 20s to early 30s.[28] It then begins to decrease. Peak bone mass as well as a number of other variables such as genetic predisposition, lifestyle, nutrition, and other secondary causes for bone loss determine the risk for osteoporotic fracture.[27,29] Thus it is difficult to isolate any single factor as the strongest determinant of fracture.

Two local studies have been performed in Hong Kong. The first was a cross-sectional, case-control study.[30] The bone density of 67 Chinese women with a mean age of 42.8 years who had used DMPA for 5 to 15 years was compared with that of 218 normal women with a mean age of 40 years. A significantly lower bone mineral density in L2-4 spine (0.93 g/cm^2), neck of femur (0.69 g/cm^2), and trochanter (0.59 g/cm^2) was observed in DMPA users compared with the control group, whose corresponding bone mineral density values were 1.03 g/cm^2, 0.83 g/cm^2, and 0.71 g/cm^2, respectively ($P<0.001$). The percentage of bone loss in L2-4 was more pronounced with age.[30] Three years later, the same group of women was reassessed[31]: 64 of 67 women could be contacted and 59 were still using DMPA. Their bone loss was substantially less than the projected loss based on the previous study. The rate of bone loss appeared to be non-linear and it was possible that the loss might level off after 5 years. These data suggest that the risks associated with long-term use of DMPA may not be as high as previously anticipated.

Safety of depot medroxyprogesterone acetate in adolescents and young women

In one cross-sectional study, no significant difference in bone mass was found in adolescent DMPA users and non-users.[32] Other studies nonetheless indicated that the use of DMPA in adolescents and young women was associated with a lower rate of bone accumulation or even modest bone loss after 1 to 2 years compared with controls.[22,33-36] Two longitudinal studies focused on 'recovery' after discontinuation of

DMPA showed that bone mineral density could recover partially or slowly.[22,36] None of these studies followed subjects long enough to assess their risk for osteoporotic fracture. There is great concern that these adolescents and young women might fail to achieve a satisfactory peak bone mass if they use DMPA for a long time. More studies are needed to broaden our understanding of the bone turnover and determine if there are any delayed sequelae of long-term DMPA use from a young age.

To strike a balance, we must highlight the importance of contraception to prevent women from getting pregnant. Depot medroxyprogesterone acetate is a very effective contraceptive with a failure rate of less than one per 100-woman-years. In the United States, availability and use of DMPA by young women has been credited, in part, with the decrease in adolescent pregnancy rates that have been observed over the past decade.[37,38]

In conclusion, DMPA may cause bone loss in long-term users and such loss may be partially reversible after cessation of use. Other risk factors for osteoporosis may also affect a person concomitantly, thus it is difficult to infer the effect of DMPA on later bone health. The potential risk of long-term DMPA use has to be balanced with the risk and consequence of an unplanned and unwanted pregnancy that may result in the absence of an effective contraceptive.

Recommendation

As a responsible service provider, we should always respect women's informed choice in selecting contraceptives based on balanced information about the pros and cons of using a given contraceptive. As the manufacturer and FDA have issued serious warnings on the safety of long-term use of the drug and may raise public concern, the Health Services Subcommittee of the Family Planning Association of Hong Kong would like to address the issue as follows:

1. When counselling women of all ages for choices of contraceptives or continuation of DMPA, the advantages and disadvantages of each birth control method should be explained in an unbiased manner to help individual women make an informed choice.
2. All women using DMPA should be advised to maintain an adequate calcium intake and exercise and to avoid risk factors for osteoporosis like smoking, alcohol, and caffeine.
3. Change from DMPA to another form of effective contraceptive should be recommended in the following situations:
   a) Women with significant risk factors for osteoporosis (eg medical history of low trauma fracture, chronic use of steroids or anticonvulsants, chronic alcohol or tobacco use, low calcium intake, sedentary lifestyle, family history of osteoporosis, anorexia nervosa/bulimia with amenorrhoea, female athletes with low bone mineral density, and women with pre-existing long-term amenorrhoea);
   b) Dual energy X-ray absorptiometry (DXA) shows a T-score of over -2.5;
   c) Women who have used DMPA for more than 2 years and are happy to use another effective contraceptive.
4. Bone mineral density measurement by DXA can be offered to women above the age of 45 years if there are other concomitant risk factors for osteoporosis (apart from long-term use of DMPA).

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