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SPECIAL ARTICLE

Effects on Lipid and Carbohydrate Metabolism and Bone Mineral Density in Acceptors Using Depot Medroxyprogesterone Actetate use as a Contraceptive

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Introduction

Depot medroxyprogesterone acetate (DMPA) is an aqueous suspension of 17- acetoxy-6 methyl progestin administered by intramuscular injection for long-term contraception.[1] In Thailand, National Family Planning Program (NFPP) has introduced DMPA to use as a contraceptive since 1970.[2] DMPA is also used in many developed and developing countries.[1] However, it is recently being approved for use in the United State and is widely being accepted by women and by their physicians.[3] Although DMPA is widely used around the world, clinical questions have arisen regarding the non-contraceptive risks and benefits. Many researchers have investigated its effects on lipid and carbohydrate metabolism as well as bone mineral density.

Pharmacokinetics of DMPA

DMPA is an effective contraceptive with very low failure rate.[4] The mechanisms of action to prevent conception are inhibition of ovulation, thick cervical mucus and unfavorable endometrium.[1] The effective contraceptive dosage of DMPA is 150 mg and is given by injection deep into the gluteal or deltoid muscle. It can prevent pregnancy as long as 90 days after injection.[1] Medroxyprogesterone acetate (MPA) can be detected in the systemic circulation within 30 minutes after its intramuscular injection and rises steadily up to more than 0.5 ng/mL, which is the effectively contraceptive blood level reached within 24 hours after the injection.[5] The level of MPA is maintained at 1.0-1.5 ng/mL for about three months, and after that it declines slowly until it is not detectable at nine months.[5] Estradiol levels are found to be in the range seen during the follicular phase.[6] It is also found that the average estradiol levels are also similar to the follicular phase during the long-term use of DMPA.[7] Even during the long-term use of DMPA, the hypoestrogenism does not occur among the acceptors and the symptoms of hypoestrogenic activity is not demonstrated.[6]

Effect of DMPA on plasma lipid levels

There have been many studies that evaluated the plasma lipids in DMPA users. An early study was reported in 1980 by Amatayalkul et al.[8] They reported on 12 Thai women who had 12-month follow-up. No effects of DMPA on triglyceride and total cholesterol were demonstrated in that study. Kremer et al[9] also conducted a cross-sectional study in 1980. Twenty-three cases of DMPA user and 23 cases of controls were recruited for the study and Kremer et al[9] found that high density lipoprotein was decreased in DMPA group when compared to a control group. In 1983, Fajumi[10] reported increasing levels of triglycerides in DMPA acceptors and decreasing levels of total cholesterol. These results contradicted the finding of Deslypere et al's[11] study in 1985. Decreasing triglyceride and high-density lipoprotein were shown in their study. Virutamasen et al,[12] reported a similar study in 1986 on 17 Thai women who were used DMPA for at

least five years and compared the group to 24 control women. The total cholesterol of DMPA users decreased when compared to the non-users. In 1991, Garza-Flores et al[13] reported the lipid levels of a small group of DMPA users and non-users in a cross-sectional study. Their study showed that the triglycerides increased and the total cholesterol and hight density lipoproteins decreased in the DMPA group. No effect of DMPA on low-density lipoprotein was reported in the study.[13] World Health Organization conducted a multicenter study on lipid metabolism in 1993.[14] Fifty DMPA users and 120 users of the intrauterine device from Mexico, New Zealand and Thailand were recruited for the study. Increasing low-density lipoprotein and decreasing high-density lipoprotein were observed in DMPA users.[14] Oyelola[15] reported a cross-sectional study of 16 DMPA users and 18 controls. DMPA users had higher mean low-density lipoprotein levels and higher mean apolipoprotein 13 levels than controls. In summary, the results of studies which evaluated plasma lipids in DMPA users are controversial. Most studies were cross-sectional and compared long-term DMPA users to age-matched non-hormonal contraceptive users. The conflicting results may be depend on the number of subjects, study design and the duration of the study. It is not possible to conclude from the available data that DMPA has unfavorable effects on lipid metabolism. A further well design study should be conducted to reevaluate the impact of DMPA on plasma lipid levels.

Impact on carbohydrate metabolism

As in women using oral contraceptives, evidence of impaired glucose tolerance is sometimes seen in DMPA acceptors.[16] In 1980, Amatayalkul et al[18] reported that DMPA users had persistently increased insulin levels during the study period, however the glucose tolerance test remained unchanged. In 1985, Lieu et al[17] studied the impact of DMPA on carbohydrate metabolism. They reported on oral glucose tolerance tests and insulin levels in 157 long-term DMPA users and 162 controls who were matched for race, age, parity and height. The mean area under the glucose tolerance test curve was slightly greater for DMPA users. However, there were no differences in mean insulin levels.

Virutamasen et al[12] also reported on DMPA and glucose metabolism in 1986. Fifty-seven Thai women who were DMPA users for at least five years and twenty-four non-users were recruited for the study. The study showed that DMPA users had abnormal oral glucose tolerance test and exhibited some return to normality within 6-23 months after discontinuing DMPA.[12] In addition, mean insulin levels were significantly higher in DMPA users than controls. However, the study of Kamua et al[18] in 1990 has shown no deterioration of glucose tolerance among the DMPA users. Even studies of the impact of DMPA on glucose metabolism have produced conflicting results, it should be carefully monitored DMPA users who had a history of diabetes, including gestational diabetes.

Bone mineral density changes

DMPA use and bone mineral density changes have recently become an interesting area of study. It is demonstrated that DMPA suppressed ovarian estradiol production. Most women who use DMPA asa contraceptive agent become amenorrheic and have hypoestrogenism.[5] It has been demonstrated that estrogen deficiency may cause osteoporosis in postmenopausal women.[19] However the effect of estrogen deficiency among the long-term DMPA acceptors on bone mineral density is still controversial.[20,22] In 1991, Cundy et al[20] reported the cross-sectional study of lumbar and femoral neck bone densities in long-term DMPA users compared with premenopausal and postmenopausal women. According to dual energy x-ray absorptiometric studies, the DMPA users had lower mean lumbar and femoral neck bone density than the age, body mass index-and race-matched premenopausal control and the postmenopausal controls, the DMPA users had greater mean lumbar and lower femoral neck bone density. However, estradiol measurement during DMPA use was not obtained.[23] Cundy et al subsequently reported on recovery of bone density in women who discontinued DMPA. Virutamasen[22] reported on a cross-sectional study in 75 Thai women DMPA users who were nonsmokers

and compared the group to 75 controls who were matched for age and weight. No significant difference in trabecular bone density in the femoral neck was demonstrated in the study.[22] However, because the bone density grading was based on x-ray films, the value of these findings is limited.[3] Naessen T et al[2] studied 22 Swedish women who were randomly assigned to begin use of either DMPA or a contraceptive implant, the bone density in the distal forearm was measured at the beginning and again at six months of the trial using single photon absorptiometry. Serum estradiol levels were also measured in these subjects. The study showed that the mean estradiol level in the DMPA users was 192 pmol/mL and the bone density of distal forearm remained unchanged over six months period.[21] Otherwise it was slightly increased in the implant group.[21] Taneepanichskul et al[7] reported on bone mineral density in long-term DMPA acceptors in 1997. Fifty healthy women who had been using DMPA for a minimum of 36 months were recruited for the study. Another 50 healthy women who had not been used any hormonal contraceptives and had been using intrauterine device were selected as control. Both groups were matched for age, parity income, weight, and height and body mass index. Bone density was measured by dual energy x-ray absorptiometry and serum estradiol levels were also measured. The study demonstrated that the mean estradiol level in the control group was significantly higher than DMPA users. However, no differences of bone mineral density in distal and ultradistal forearm between the two groups were demonstrated. Taneepanichskul et al[24] subsequently reported a cross-sectional study of bone density in long-term DMPA and Norplant® users. It was shown that bone mineral density was not different between DMPA and Norplant® acceptors.

Conclusion

DMPA is highly effective injectable method of contraception. Despite many years of widespread use of DMPA contraception among 30 million women worldwide in more than 90 countries, case reports of adverse clinical events are conspicuously absent from the medical publications.[3, 16] Most of the literature reviews reveal some adverse changes in serum lipids that are considered predictors of atherosclerosis, glucose metabolism and bone mineral density. However, the results of studies show conflicting finding. Epidemiologic data regarding the long-term risk of fracture, diabetes mellitus or heart disease in DMPA acceptors are not available. Until more knowledge is gained, DMPA users should receive standard counseling about diet, exercise and smoking behavior changes that will minimize their cardiovascular and osteoporotic fracture risks. It should be also carefully screened and monitored DMPA user who had history of diabetes and other risk factors for carbohydrate and lipid metabolic disorders.

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