

Effects of Long-term Treatment with Depot Medroxy Progesterone Acetate for Contraception on Estrogenic Activity

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Abstract

The aims of this study were to evaluate the serum estradiol level and the estrogenic activity in long-term DMPA users. From 1st January 1996 to 31st December 1996, fifty healthy women receiving DMPA for contraception for more than 36 months were recruited to the study. From the study, it was found that the mean duration of DMPA use was 59.1 ± 30.7 months, the mean serum estradiol was 52.7 ± 15.1 pg/ml and these women did not have problems of estrogen deficiency. This study revealed that long-term treatment with DMPA should not have any adverse effects on estrogenic activity.

Depot medroxy progesterone acetate (DMPA) is an aqueous suspension of 17-acetoxy-6-methyl progestin administered by intramuscular injection for contraception⁽¹⁾. It has been used by 30 million women in more than 90 countries⁽²⁾. The recommended dosage is 150 mg intramuscularly every 3 months⁽²⁾. Almost all users experience menstrual changes during the first year of use⁽²⁾. With continued use, irregular vaginal bleeding decreases, and amenorrhea becomes common⁽²⁾. Following an injection of DMPA, the mean serum estradiol levels are in the early to mid follicular phase range and the endometrium

becomes atrophic⁽²⁻⁴⁾. However, the estrogenic activity in long-term acceptors is not well investigated. The objective of this study was to evaluate the serum estradiol level in long-term DMPA users.

MATERIAL AND METHOD

Fifty healthy women aged 24-48 years who had been using 150 mg injection of DMPA every 12 weeks for contraception with a minimum period of 36 months and attended the Family Planning Clinic, Department of Obstetrics and Gynaecology, Ramathibodi Hospital, Bangkok from

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1st January 1996 to 31st December 1996 were recruited. None had any history of smoking, alcohol intake, endocrine disorder or had an illness or took drugs known to affect endocrine function. All active acceptors were examined by the authors at the time of their scheduled visit for injection. They were interviewed about possible subjective effects associated with a significant diminution in circulating estrogen levels. Each patient was asked whether she had dryness of the vagina, hot flushes or night sweating. The serum estradiol concentration was obtained from each of these women at this time and was measured by microparticle enzyme immunoassay (MEIA) technique using the Abbott IMx® immunoassay automation, U.S.A. Our laboratory value for normal estradiol levels in the early follicular phase are 25-221 pg/ml. In the midcycle peak and the luteal phase are 83-690 and 26-408 pg/ml respectively. In menopausal women, the value of serum estradiol is below 25 to 86 pg/ml. This technique has low cross-reactivity with other compounds. All data were collected, coded and analyzed by the investigators. SPSS/PC+ for Windows, a statistical package program, was used to analyze data. Statistical values employed were mean, standard deviation, Pearson product moment correlation coefficient and 95 per cent confidence interval. The significant level considered was at 0.05.

RESULTS

The characteristics of DMPA users are shown in Table 1. Their mean age \pm SD was 32.9 ± 5.7 years and their mean body mass index (BMI) \pm SD was 23.9 ± 3.9 kg/m². The mean duration of DMPA use \pm SD was 59.1 ± 30.7 months with minimum 36 months and maximum 168 months. The mean serum estradiol \pm SE was 52.7 ± 15.1 pg/ml (range 25.9-124.4 pg/ml). The correlation coefficient between the serum estradiol and duration of DMPA use was 0.11 and had no statistical significance ($P > 0.05$). Considering the possible symptoms related to estrogen reduction, these women did not have problems with vaginal dryness, hot flushes or night sweating. On examination of the breasts, none of these acceptors had any nodules or palpable tumors. Upon pelvic examination, all of them had moist and well-rugated vaginal mucosa.

Table 1. Characteristic of DMPA users.

Characteristics	DMPA users (n=50)	95% CI
Age (year)	32.9 ± 5.7 (range 24-48)	31.3, 34.5
Parity	1.4 ± 0.5 (range 1-2)	1.26, 1.54
Bodyweight (kg)	57.4 ± 9.3 (range 42.2-79)	54.8, 60
Height (cm)	155.2 ± 4.9 (range 142-169)	154, 157
Body mass index (kg/m ²)	23.9 ± 3.9 (range 17.4-32.9)	22.8, 25

DISCUSSION

DMPA is a highly effective injectable method of contraception⁽²⁾. Its contraceptive effect results from inhibition of ovulation⁽²⁾. After the administration of DMPA, plasma levels of follicle-stimulating hormone and luteinizing hormone decline, and luteinizing hormone surges do not occur⁽¹⁾. Mishell et al⁽³⁾ reported that circulating estradiol levels during the first two months after the initial 150 mg injection of DMPA were similar to the levels found in the follicular phase of the normal menstrual cycle. Jeppsson⁽⁴⁾ also reported the same results. However, these serum estradiol levels were found in short period DMPA users. The serum estradiol concentration in long-term DMPA users has never been well investigated. This study revealed the serum estradiol in long-term treatment with DMPA for contraception. The duration of DMPA use was more than 36 months and the maximum period of DMPA treatment was 168 months. From the study, it was found that the serum estradiol levels were in the follicular phase of the normal menstrual cycle and were not different from short-term users⁽³⁾. The estradiol level is higher than postmenopausal women⁽³⁾. This evidence suggests that women receiving long-term DMPA treatment for contraception have functioning ovaries which continue to secrete estradiol at levels greater than those found in post menopausal women but less than those of ovulating women. The lack of subjective symptoms of hypoestrogenism reported by these women agrees with those serum estradiol findings. The study also revealed no significant correlation between period of DMPA

treatment and serum estradiol concentration. This evidence also suggested that long-term treatment with DMPA should not have accumulation of the preparation in the body(5).

In conclusion, this study revealed that long-term DMPA acceptors had no symptoms of estrogen deficiency and their serum estradiol levels

were well above the postmenopausal women. It is suggested that the addition of exogenous estrogens for long-term DMPA users is not necessary. However, this study is a cross-sectional design which has some limitations to interpret the results. A further prospective cohort study should be conducted to verify these findings.

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REFERENCES

1. Mishell DR, Jr. Pharmacokinetics of depot medroxyprogesterone acetate contraception. *J Reprod Med (suppl)* 1996; 41: 381-90.
2. Kaunitz AM. Long-acting injectable contraception with depot medroxy progesterone acetate. *Am J Obstet Gynecol* 1994; 170: 1543-9.
3. Mishell DR, Jr, Kharma KM, Thorneycroft IH, Nakamura RM. Estrogenic activity in women receiving an injectable progestogen for contra-ception. *Am J Obstet Gynecol* 1972; 113: 372-6.
4. Jepsson S, Johansson ED, Sjoberg NO. Plasma levels of estrogens during long-term treatment with depo-medroxy progesterone acetate as a contraceptive agent. *Contraception* 1973; 8: 165-70.
5. Goldzieher JW, Kleber JW, Moses LE, Rathmacher RP. A cross-sectional study of plasma FSH and CH levels in women using sequential, combination or injectable steroid contraceptive over long period of time. *Contraception* 1970; 2: 225-47.

ผลของการใช้ยาฉีดคุมกำเนิด ดีเอ็มพีเอ เป็นระยะเวลานานต่อระดับเอสโตรเจน

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ยาฉีดคุมกำเนิด DMPA เป็นยาฉีดคุมกำเนิดที่ใช้กันแพร่หลายทั่วไปและมีประสิทธิภาพสูง กลไกที่สำคัญในการป้องกันการตั้งครรภ์คือ การยับยั้งการตกไข่ ทำให้ไข่บุปผงมดลูกฟ่อเมื่อใช้เป็นระยะเวลานาน ทำให้ไม่มีประจำเดือนและมีภาวะ estrogen ต่ำ การศึกษานี้มีวัตถุประสงค์ เพื่อศึกษาถึงระดับของ estradiol ในเลือดและ estrogenic activity ในสตรีที่ใช้ DMPA เป็นระยะเวลานาน โดยทำการศึกษาในสตรีที่ใช้ DMPA จำนวน 50 ราย โดยมีระยะเวลาที่ใช้ DMPA ตั้งแต่ 36 - 168 เดือน ที่คลินิกวางแผนครอบครัว ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี จากการศึกษาพบว่า สตรีที่ทำการศึกษามีอายุเฉลี่ย 32.9 ± 5.7 ปี มีระยะเวลาในการใช้ DMPA 59.1 ± 30.7 ปี มีระดับ estradiol ในเลือด 52.7 ± 15.1 pg/ml. และสตรีทุกรายไม่มีอาการของการขาดออกอ่อน estrogen นอกจากนี้ไม่พบความสัมพันธ์ระหว่างระยะเวลาที่ใช้ DMPA กับระดับ estradiol ในเลือด ($r=0.11$ $P>0.05$) จากการศึกษาสรุปได้ว่า การใช้ DMPA เป็นระยะเวลานาน ไม่มีผลผลกระทบต่อ estrogenic activity.

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