Plasma levels of medroxyprogesterone acetate (MPA), sex-hormone binding globulin, gonadal steroids, gonadotrophins and prolactin in women during long-term use of depo-MPA (Depo-Provera®) as a contraceptive agent

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Abstract. The aim of the study was to evaluate the functional state of the hypothalomo-pituitary-gonadal axis and to assess the concentrations of MPA in the peripheral blood during very long-term use of depo-medroxyprogesterone acetate (DMPA) as a contraceptive agent.

The concentrations of MPA, sex-hormone binding globulin (SHBG) and the different pituitary and gonadal hormones in the peripheral blood were measured in nine 26–41 year old women. They had for 4.4–10.6 years (mean 8.9 years) been receiving DMPA im in a dose of 150 mg every 12th week as a contraceptive. Blood samples were obtained immediately before an injection of DMPA, 2 weeks later, and again immediately before the next injection. SHBG was measured by radio-electro-immunoassay; MPA, gonadal and pituitary hormones by RIA.

The investigation showed that the oestradiol levels – even after very long-term use of DMPA – were still within the normal range for the early follicular phase. Gonadotrophins and prolactin were within the normal range for eumenorrhoeic women as well as the concentration of SHBG. MPA did not accumulate in the plasma. The changes in the plasma levels of oestradiol, MPA and SHBG after each injection disappeared within 12 weeks. The study appears to warrant the conclusion that even up to 10 years’ use of DMPA in a dose of 150 mg im every 12th week as a contraceptive agent, does not induce hormonal changes different from those seen after the very first injection.

Depo-medroxyprogesterone acetate (DMPA) is a microcrystalline suspension of medroxyprogestrone acetate. It is marketed (Depo-Provera®, Upjohn Company) in many countries as an injectable contraceptive. It is administered in a dose of 150 mg every 12th week. DMPA is the most widely used compound for contraception by long-acting pure gestagen injections and has been available for about 15 years.

Its efficacy, acceptability and side effects are well documented (Hammerstein 1972; Mishell 1974; Rosenfield 1974; Schwallie 1974; Schwallie & Assenzo 1974; Nash 1975; Rinehart & Winter 1975; WHO 1977, 1978). DMPA in the above mentioned dose inhibits follicular growth and ovulation. As an additional contraceptive effect, DMPA exerts a progestational action on the cervical mucus and the endometrium. The drug is well tolerated and has few side effects. The vaginal bleedings are unpredictable as no distinct withdrawal of DMPA occurs. However, the unpredictable uterine bleeding episodes gradually cease and after one year’s use 35–50% of the women are amenorrhoeic (Jeppsson 1972; WHO 1978).

Although there is an abundance of clinical data about women using DMPA as a contraceptive agent, our information is limited to the variations in gonadal and pituitary hormones as well as to the plasma concentrations of MPA in women using DMPA for a very long time.

The aim of this study was to evaluate the functional state of the hypothalomo-pituitary-gonadal
axis and to measure the plasma levels of MPA and SHBG in women with amenorrhoea induced by the use of DMPA as a contraceptive agent for up to 10 years.

**Material and Methods**

The material consisted of nine 26-41 year old amenorrhoeic women who had received constant treatment with DMPA im in a dose of 150 mg every 12th week for 4.4-10.6 years (mean 8.9 years). Blood samples were obtained from an antecubital vein immediately before and 2 weeks after an injection of DMPA, and again immediately before the next injection. The first and the third samples were thus identical in relation to the injection of DMPA. On the third sampling occasion it was possible to obtain blood in only 7 of the 9 women. The blood was collected in tubes containing EDTA as anticoagulant. The samples were centrifuged and the plasma was removed and stored at -20°C until analysed.

In all blood samples the following analyses were performed:

Medroxyprogesterone acetate was measured by radioimmunoassay (RIA) according to Jeppsson & Johansson (1976).

Oestradiol-17β (Oe2) was measured by RIA according to Edqvist & Johansson (1972) and Oestrone (Oe1) according to Axelsson et al. (1978).

The protocols of the RIA of testosterone, progesterone,

![Graph](image_url)

**Fig. 1.**

Mean plasma concentrations (± se) of MPA, SHBG, gonadal and pituitary hormones in 9 women using DMPA 150 mg im every 12th week for contraceptive purposes. Blood samples were drawn during a 12 week period, after 4.4-10.6 years’ use, immediately before an injection (0 weeks), 2 weeks later (2 weeks), and immediately before the next injection (12 weeks).
**Table 1.**

Mean plasma levels of MPA, SHBG, gonadal and pituitary hormones in 9 women during long-term (4.4–10.6 years) use of DMPA in a dose of 150 mg every 12th week. Blood samples were obtained immediately before an injection of DMPA (1st sample), 2 weeks later (2nd sample), and immediately before the next injection (3rd sample).

<table>
<thead>
<tr>
<th></th>
<th>1st sample</th>
<th>2nd sample</th>
<th>3rd sample</th>
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<tbody>
<tr>
<td></td>
<td>(n = 9)</td>
<td>(n = 9)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td><strong>MPA nmol/l</strong></td>
<td>1.7 ± 0.3</td>
<td>6.8 ± 0.8</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td><strong>Oestradiol pmol/l</strong></td>
<td>374 ± 31.4</td>
<td>243 ± 19.6</td>
<td>342 ± 35.8</td>
</tr>
<tr>
<td><strong>Oestrone pmol/l</strong></td>
<td>339 ± 20.1</td>
<td>263 ± 17.7</td>
<td>360 ± 12.4</td>
</tr>
<tr>
<td><strong>SHBG % of normal pool</strong></td>
<td>104.4 ± 5.9</td>
<td>89.0 ± 5.2</td>
<td>103.9 ± 9.4</td>
</tr>
<tr>
<td><strong>Testosterone nmol/l</strong></td>
<td>1.8 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td><strong>FSH µg/l</strong></td>
<td>2.2 ± 0.3</td>
<td>3.3 ± 0.2</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td><strong>LH µg/l</strong></td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td><strong>Prolactin µg/l</strong></td>
<td>10.2 ± 6.0</td>
<td>11.3 ± 1.2</td>
<td>10.7 ± 1.3</td>
</tr>
<tr>
<td><strong>Progesterone nmol/l</strong></td>
<td>&lt; 2.0 –</td>
<td>&lt; 2.0 –</td>
<td>&lt; 2.0 –</td>
</tr>
</tbody>
</table>

Follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin have been described elsewhere (Thorell & Larsen 1978).

Sex-hormone-binding globulin (SHBG) was measured by a new radio-electroimmunoassay (Fernlund et al., submitted). Intra- and inter-assay variations were < 5%. Values are given as percentages of a standard plasma pool from 30 healthy normally menstruating women.

Albumin was determined by a brom-cresol method.

Results

The variations in plasma concentrations of MPA, oestradiol, oestrone, SHBG, testosterone, FSH, LH and prolactin during the 12 week study period are shown in Fig. 1 and Table 1.

Plasma oestradiol decreased slightly (P < 0.025) within 2 weeks of the injection of DMPA, while oestrone did not change significantly (P > 0.05). All the levels were within the normal range for the early follicular phase.

The concentration of testosterone was within the normal range and showed no significant differences.

The plasma levels of FSH and LH were within the normal range for eumenorrhoeic women (< 3.5µg/l). The prolactin levels were normal.

The SHBG levels corresponded to those in eumenorrhoeic women (104 ± 6% of normal pool) (mean ± SE) and decreased significantly to 89 ± 5% (P < 0.001) by 2 weeks after the injection of DMPA.

At the initial examination the concentration of MPA was 1.7 ± 0.3 nmol/l. Two weeks after the injection of DMPA it was 6.8 ± 0.8 nmol/l (P < 0.001).

The plasma concentration of progesterone was invariably below 2 nmol/l.

The plasma albumin concentrations were within normal limits without significant changes throughout the observation period.

No significant difference was found between the initial plasma levels and those found 12 weeks later apart from a slight increase of FSH within the normal range.

Discussion

The plasma concentration of MPA was significantly higher 2 weeks after injection of 150 mg DMPA compared to the pre-injection level, but fell to the initial concentration by the end of the 12 week period. The mean concentration of MPA at the end of a 12 week period in this study was 1.7 and 1.2 nmol/l, respectively. These levels are almost identical with those measured with the same RIA-technique in corresponding blood samples from women who had received the same treatment with DMPA but for a considerably shorter period of time – about 3 years (Jeppsson et al. 1977). The levels were also similar to those found by Ortiz et al. (1977) in 3 women 90 days after a single injection of DMPA. They measured MPA with a RIA-techni-
que giving results comparable to ours. Thus, the level of MPA in the peripheral blood at the end of a 12 week period does not vary with the number of injections and thereby indicates the absence of accumulation of MPA in the peripheral blood. This agrees with the clinical finding that resumption of ovulatory cycles after discontinuation of DMPA treatment is unrelated to the number of injections (Schwallie & Assenzo 1974). Though available reports do not allow careful comparison between the peak levels of MPA in the first weeks after different numbers of injections of DMPA, they do suggest (Jeppsson et al. 1977; Jeppsson & Johansson 1976; Ortiz et al. 1977; Fotherby et al. 1980) that the peak levels do not increase with increasing number of injections.

DMPA in a dose of 150 mg im effectively inhibits ovulation, but the mode of action by which DMPA blocks ovulation is not clearly understood. It is generally claimed that the action is a central inhibition of the gonadotrophins. But, except for the mid-cycle peak, previous investigations (Mishell et al. 1972; Goldzieher et al. 1970; Jeppsson & Johansson 1976; Jeppsson et al. 1977) as well as the present study, have not found the plasma concentrations of FSH or LH to be lower than in eumenorrhoeic women. Furthermore, the LH and FSH responses to GnRH differ only slightly from those in eumenorrhoeic women in the luteal phase (Robyn et al. 1978; Mishell et al. 1977). However, judging from the oestradiol levels, follicular maturation does not occur (Mishell et al. 1972; Jeppsson et al. 1973; Jeppsson & Johansson 1976; Ortiz et al. 1977).

The present study shows that oestradiol levels are in the range of the normal early follicular phase, indicating that no further suppression of the gonadal secretion of oestradiol occurs even after 10 years' use of the drug. Furthermore, this study corroborates the previous observation by Jeppsson et al. (1973) of a significant decrease in oestradiol during the first weeks after a few injections of DMPA and a subsequent rise at the end of the 12 week period. The oestrone levels paralleled those of oestradiol and the quotient between Oe₂ and Oe₁ was not that found in post-menopausal women.

The inhibitory effect of 150 mg DMPA im on ovulation lasts for at least 12 weeks and mostly still longer. Our findings agree with those reported by Ortiz et al. (1977) and to some extent also with those of Fotherby et al. (1980) in that oestradiol levels consistent with full follicular maturation were not seen until the MPA levels in plasma were below 1.3 nmol/l (approximately 0.5 ng/ml). This is in good agreement with observations by Victor & Johansson (1976) during administration of MPA by intravaginal rings. In the study of Ortiz et al. (1977), oestradiol peaks up to pre-ovulatory levels were not, however, followed by subsequent progesterone rise suggesting ovulation before the MPA level had fallen further down to 0.3 nmol/l (approximately 0.1 ng/ml). They did not find such progesterone levels until 7–9 months after a single injection of 150 mg DMPA in 3 women studied, and similar results have recently been published by Fotherby et al. (1980). In both these reports there was a close correlation between the disappearance of MPA from the circulation and the return of ovulatory cycles.

The absence of ovulation in spite of pre-ovulatory oestradiol levels is most likely due to inhibition of the positive feed-back of oestradiol – caused by very low levels of circulating MPA – at the hypothalamus with consequent prevention of the mid-cycle surge of LH. This phenomenon has previously been observed with other forms of administration of gestagens producing low circulating levels of the steroid (Weiner et al. 1976).

Using a testosterone-binding method, Ettinger & Golditch (1977) found a small decrease in SHBG-capacity, which did not reach statistical significance. The women in that study were treated with 10 mg MPA orally, 3 times daily, for 3 months or more. Other investigators (Gordon et al. 1970; Forest & Bertrand 1972), who also used binding techniques, found a similar decrease in the concentration of SHBG in MPA-treated women. In our study the mean value immediately before injection corresponded to that of the normal pool. Two weeks after the injection, SHBG concentrations were approximately 15% lower and the difference was significant ($P < 0.001$).

The present study appears to warrant the conclusion that even up to 10 years' use of DMPA in a dose of 150 mg im as a contraceptive agent, does not induce hormonal changes different from those seen after the very first injection.

References


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