POSTPONEMENT OF MENSES, SUPPRESSION OF URINARY GONADOTROPHINS, 17-KGS AND 17-KS IN NORMAL WOMEN TREATED WITH A MEGESTROL ACETATE / MESTRANOL COMBINATION (DELPREGNIN) FROM DAY 20 OF THE CYCLE

By

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ABSTRACT

Ten normally menstruating women, ranging in age from 19–32, received 5 mg of megestrol acetate plus 0.1 mg of mestranol from day 20 of the cycle daily for 20 days. Individual 48 h urine collections were obtained from cycle days 7–8, 13–14, 18–19, and from days 9–10 and 19–20 during the treatment. Each 48 h specimen was assayed for total gonadotrophins, 17-KGS and fractionated 17-KS. The basal temperature and occurrence of menstruation were noted before, during and after the treatment.

In 7 cases unequivocal suppression of gonadotrophins was observed during the medication period, and all these women had their expected menstruation postponed until after termination of the treatment. The next menstrual cycles were ovulatory and regular in relation to the postponed menstruation. In 3 cases no suppression of gonadotrophins was observed and these same cases had no postponement of menstruation.

The mean excretion of 17-ketogenic steroids and of 17-ketosteroids (total 17-KS, dehydroepiandrosterone, androsterone and aetiocholanolone frac-

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tions) in the whole group was significantly depressed at the end of the treatment period.

Megestrol acetate (6-dehydro-6-methyl-17-acetoxyprogesterone) has been synthesized by Kirk et al. (1958) and by Ringold et al. (1959). Pharmacological studies carried out by Elton et al. (1960), David et al. (1963) and Kincl (1961) have shown that megestrol acetate given orally is a very effective gestagen, without any androgenic or anabolic properties. In rabbits, it has a marked inhibitory effect on ovulation. Clinical studies by Østergaard (1965) have shown that megestrol acetate given by mouth has the usual properties of progesterone, and a dose of 2.5–5 mg a day for 10 days is sufficient for the production of a normal secretory phase in an oestrogen primed endometrium of amenorrhoeic women. The combination of megestrol acetate with the oestrogen mestranol (ethinyloestradiol-3-methyl-ether) is a reliable ovulation inhibitor as shown in ad hoc planned laparotomies (Østergaard 1964). Greenblatt et al. (1958) and Swyer & Little (1962) have observed postponement of menses when an appropriate dose of a gestagen with added oestrogen is given from the 20th day of the cycle, and this has been used by the above named authors as a comparative test for progestational activity.

The purpose of the present investigation has been to elucidate the capacity of megestrol acetate to postpone menses when given in combination with mestranol from the 20th day of the cycle. At the same time it was intended to investigate the effect of this treatment on the excretion of gonadotrophins, 17-ketosteroids (17-KS) and 17-ketogenic steroids (17-KGS).

MATERIAL AND METHODS

Ten normally menstruating women volunteered for this investigation. They received the combined gestagen/oestrogen preparation Delpregnin®, one tablet a day for 20 days, treatment starting 10 days before the expected time of the next menstruation. Each Delpregnin tablet contains 5 mg megestrol acetate + 0.1 mg mestranol.

Fig. 1 gives information on the age and menstrual cycles of the subjects and the plan of the investigation. The age ranged between 18 and 32 years, and the cycle length, indicated in the first column of open rectangles, varied between 26 and 36 days. Nine of the ten subjects had very regular menstruations.

The open rectangles represent the expected menstruations without any treatment and the hatched rectangles represent the observed menstruations or bleedings before, during and after the treatment. Individual 48 h urine specimens were obtained from day 7–8, 13–14, 18–19 (or one day later in prolonged cycles) and subsequently from day 9–10 and 19–20 of the treatment period.

The urine specimens were assayed for total gonadotrophins by the method of Johnsen (1958), for 17-KGS by the method of Appleby et al. (1955) as modified by Jørgensen (1957) and for total fractionated 17-KS by the method of Johnsen (1956). Basal temperature charts were registered throughout the investigation period.
Postponement of menstruation induced by treatment with megestrol acetate 5 mg plus mestranol 0.1 mg per day from Day 20 of the cycle.
RESULTS

Fig. 1 gives the result as regards postponement of menses. It is seen that the seven subjects shown below had their menses delayed until after the end of the period of treatment. The displacement of the cycle is retained throughout the following months. From the temperature charts it was justifiable to assume that ovulation occurred between 2 and 3 weeks after the last tablet had been taken. The three subjects shown above had their menstruation at or very close to the expected time in spite of the treatment. All three women experienced a short bleeding after termination of the treatment, presumably a withdrawal bleeding. The next ovulation and menstruation was also somewhat delayed in these cases, but not very much.

Fig. 2 shows the excretion of gonadotrophins before and during the treat-

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**Fig. 2.**

Urinary «total» gonadotrophins per day before and during treatment with megestrol acetate 5 mg plus mestranol 0.1 mg per day from Day 20 of the cycle.

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ment in the 7 women who had their menstruation delayed. The values represent »total« gonadotrophins expressed in mouse uterus units (M. U. U.) per day. On days 7–8, 13–15 and 18–19 of the cycles (i.e. before the treatment), the values are within the normal range. In the course of the treatment, the excretion is markedly depressed, in 5 of the 7 cases even to values below the sensitivity limit of the method.

The excretion of gonadotrophins in the 3 women without postponement of menses is shown in Fig. 3. It is seen that no suppression of the excretion occurred.

In Table 1 the individual initial values of the gonadotrophin excretion are compared with those obtained 21 and 31 days later. The difference between the groups of women with and without postponement of menses is obvious.

In Fig. 4 are seen the values for the excretion of 17-KGS in mg/d for all

![Diagram](https://via.placeholder.com/150)

Fig. 3.

Urinary »total« gonadotrophins per day before and during treatment with megestrol acetate 5 mg plus mestranol 0.1 mg per day from Day 20 of the cycle.
Table 1.
Urinary excretion of gonadotrophins in all cases (M. U. U./d).

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Gonadotrophin excretion</th>
<th>Onset of next menstruation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>initially</td>
<td>during treatment</td>
</tr>
<tr>
<td>AMØ</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td>EA</td>
<td>18</td>
<td>&lt;6*</td>
</tr>
<tr>
<td>DC</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>AGMC</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>ID</td>
<td>10</td>
<td>&lt;3</td>
</tr>
<tr>
<td>KT</td>
<td>13</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Al</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>WN</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>JS</td>
<td>17</td>
<td>&lt;12**</td>
</tr>
<tr>
<td>BP</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Mean</td>
<td>11.3</td>
<td>21.3</td>
</tr>
</tbody>
</table>

* the highest dose of the extract was toxic.
** the two highest doses of the extract were toxic.

ten subjects on the above mentioned days, i. e. before and during treatment. A slight but unquestionable fall in the values is seen during the treatment, but only in one case to values below the normal range. The 3 cases without postponement of menses (indicated by »fat« drawing of the curve) do not differ from the others in this respect.

Fig. 5 shows the excretion of total 17-KS in mg/day on the same days as above. Here too, there is a slight but unquestionable suppression to lower values. The uppermost curve represents one of the three cases without postponement of menses. It is 5-6 mg/d higher but parallel to the average excretion for the others. This woman (BP) with rather high values for 17-KS excretion did not show any symptoms indicating adrenocortical or ovarian disease. The two other subjects without any delay of menses do not differ from the other cases.

In Table 2 a comparison is made of the mean excretion of 17-KGS and 17-KS on days 8–9 of the cycles and on days 18–19 after the beginning of the treatment, i. e. about 30 days later. The mean differences with their standard deviations and the P-values are calculated. In all instances the depression of the steroid excretion is statistically significant.
Fig. 4.
Urinary 17-ketogenic steroids per day before and during treatment with megestrol acetate 5 mg plus mestranol 0.1 mg per day from Day 20 of the cycle.

All 10 volunteers were controlled 1 to 2 months later, and at that time 9 of them had the same levels of 17-KS and 17-KGS as before treatment; one was a little lower but within the normal range.

DISCUSSION

In this investigation we have demonstrated postponement of menses in seven of ten women treated with one Delpregnin tablet a day from about the 20th day of the cycle. In the clinical study published by Østergaard (1965) postponement of menses was obtained in nineteen of twentythree women similarly treated, and in all of the eight women who received 2 tablets a day from the 20th day.

In order to obtain a reliable postponement of menstruation 2 tablets a day
corresponding to 10 mg megestrol acetate + 0.2 mg mestranol, should be given, which is in accordance with the experience of Greenblatt et al. (1963) as regards this gestagen/oestrogen combination.

As to the hormone excretion studies, a complete control cycle before and after the period of treatment might have been preferable. However, the values obtained on day 19-20 during the treatment are comparable to the values from day 7-8 before the treatment, as they are obtained 30-31 days later and from the same days of the following cycle.

It is also well known from the studies of Johnsen (1959) that the daily variations in the excretion of total gonadotrophins are considerable, the highest
values occurring near mid-cycle, but values below 3 M. U. U./day are quite exceptional in normal cycles. We therefore consider the substantial reduction in gonadotrophin excretion observed at the end of the treatment in most of our cases, as actually resulting from the treatment.

The suppression of gonadotrophins in most of our cases is remarkable and not in agreement with some other investigators, e.g. Albert & Smith (1961), Brown et al. (1962) and Loraine (1964). These authors find no suppression of gonadotrophins during treatment with several other gestagens or gestagen/oestrogen combinations. On the other hand, Hamburger & Sprechler (1951), Pincus (1957), Heller (1957), Kuppermann & Epstein (1957), Martin & Cunningham (1961), Buchholz et al. (1964), Demol & Ferin (1964), Erb & Keller (1964), Walser et al. (1964) and Østergaard (1965) have, under somewhat similar conditions, demonstrated more or less regularly a reduction or a suppression of the gonadotrophins. There may be several causes for this discrepancies, e.g. differences in the extraction and assay methods, and in the type and mode of administration of the gestagen/oestrogen combinations used.

Variations in the excretion of 17-KS and 17-KGS relative to the menstrual cycle have been postulated by some authors (Puck et al. 1952; Ikegawa 1958) and denied by others (Werner 1941; Sprechler 1951; Borth et al. 1957).

The moderate but significant suppressions of 17-KGS and 17-KS observed at the end of the treatment period in our cases are based upon values from the same days of the cycle and therefore independent of eventual cyclic variations in the excretion.

A moderate depression of 17-KS and 17-KGS during gestagen/oestrogen treatment has also been observed by Pincus (1957), Wallach et al. (1963), Vanek (1964) and Mauvais-Jarvis et al. (1965).

### Table 2.
Mean excretion of 17-KGS and 17-KS in the whole group before and towards the end of treatment.

<table>
<thead>
<tr>
<th>Steroids assayed</th>
<th>Mean excretion (mg/d)</th>
<th>Mean of diff.</th>
<th>SD of diff.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>days 8 + 9 of the cycle</td>
<td>days 18 + 19 during treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-KGS</td>
<td>9.3</td>
<td>6.2</td>
<td>3.13</td>
<td>2.9</td>
</tr>
<tr>
<td>17-KS total</td>
<td>10.2</td>
<td>6.5</td>
<td>3.64</td>
<td>2.1</td>
</tr>
<tr>
<td>DHEA-fraction</td>
<td>1.29</td>
<td>1.01</td>
<td>0.27</td>
<td>0.33</td>
</tr>
<tr>
<td>Androst.-fraction</td>
<td>2.16</td>
<td>1.39</td>
<td>0.77</td>
<td>1.08</td>
</tr>
<tr>
<td>Aetiochol.-fraction</td>
<td>2.77</td>
<td>1.34</td>
<td>1.43</td>
<td>1.06</td>
</tr>
</tbody>
</table>
None of our volunteers or patients showing such a depression of 17-KS and 17-KGS developed any symptoms suspicious of adrenal insufficiency.

In women treated for longer periods with Delpregnin, until suppression of total gonadotrophins and reduction of 17-KGS occurred, Starup et al. (1965) found no suppression of the hypophyseal ACTH response in the metopirone test, as might be suspected, and the adrenal response to ACTH stimulation was normal. Wallach et al. (1963) also found a normal adrenal response to ACTH during Enovid® therapy.

Hence, other factors, as for instance changes in the proteinbinding or metabolism of corticoids, might be responsible.

The slight depression in androsterone- and aetiocholanolone fractions, also evident in the investigations of Vanek (1964) and Mauvais-Jarvis (1965), may be considered as resulting from inhibition of the gonadotrophic stimulation of the ovary.

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