OESTROGEN EXCRETION DURING CORTISONE THERAPY

By

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The relationship between adrenal cortical function and the production of oestrogenic hormones is in many respects unclear. The concepts of the different authors as to the effect of adrenal steroids on the female reproductive system do not agree very well. Only limited facts are existing e.g. with regard to the effect of cortisone on the production and release of pituitary gonadotrophins. Further it is well known that a considerable production of oestrogenic steroids may take place in extraovarian tissues in pathological conditions as well as after bilateral oophorectomy. However, it is still unknown in what degree oestrogenic steroids are formed in the adrenal cortex in fertile women under normal circumstances.

In spite of the extensive therapeutic use of steroids from the cortisone group, still little is known as to the effect of this therapy on the female reproductive functions. While menstrual disturbances resulting from cortisone administration have been reported in certain cases (Hench et al., 1950), on the other hand, stimulation of ovarian hormone production as a response to cortisone therapy seems to be well established (Greenblatt, 1953; Jones et al., 1953). The pituitary gonadotrophic activity and the gonadotrophin titer of the urine may be elevated as a result of cortisone administration (Sohval & Soffer, 1951; Maddock et al., 1953; Moore, 1953; Blivaiss et al., 1954). Therefore the hypothesis has been put forward, that a depressed corticotrophin production allows the gonadotrophic activity to increase. Hirsute women with menstrual irregularities and sterility have in certain cases been shown to be amenable to cortisone therapy. Increased menses, induction of ovulatory cycles, and conception have in several cases occurred in such patients as a result of this form of treatment. A slight modification in the hirsutism has also been noted.

Investigations have been made on the effect of cortisone therapy on the excretion of urinary oestrogens in castrated breast cancer patients (Smith &
Emerson, 1954), but, to our knowledge, no such studies have been reported in cortisone treated women with intact ovaries. The following short communication presents the results from urinary oestrogen determinations performed in a hirsute woman, who was treated for 11 months with cortisone. Our material comprises only one single individual, and for this reason our results are not conclusive. We hope, however, to extend the investigation, in order to complete the results of this preliminary communication.

CASE RECORD

The patient was a 24-year-old nurse. She had no obesity. Her weight was 62 kilograms and her height 170 centimeters. She had never been pregnant. Since her fourteenth year she had always menstruated regularly, with bleeding periods of 4 days and 32 days' cycles. There was slight dysmenorrhoea. During the last two years before treatment she developed increasing hirsutism of virile type, which at the time of investigation was particularly pronounced in the face, on the breasts, abdomen, and the lower extremities. Otherwise her growth of hair was normal. There was no hirsutism among the relatives. The thyroid was normal and the B. M. R. was 103 per cent. X-ray examinations showed no signs of enlargement of the sella turcica or the adrenals. The urine was physiological. The genital organs were quite normal. Especially the ovaries were found to be of normal size during the whole observation time, as judged by several palpations. The woman

![Fig. 1](https://www.bioscientifica.com)

Excretion of 17-ketosteroids before and during cortisone therapy in a 24-year-old woman with hirsutism. The dotted lines represent the upper and lower limits of the normal variation range.
refused to let us take specimens from the endometrium. However, the basal temperature was registered during the whole observation time and showed ovulation. Besides she had dysmenorrhea at every menstruation as a sign of ovulation. The gonadotrophin titer of the urine was normal. The 17-ketosteroids were slightly elevated, and fell to normal, and even subnormal levels during treatment (Fig. 1). The patient felt well during the cortisone treatment and her menstruations were continually regular and normal. The cortisone dosage was started with 50 mg. orally per day, was for a short period lowered to 25 mg., but had to be increased gradually to 100 mg. daily. During the treatment the hirsutism decreased on the abdomen and the lower extremities, but not in the face.

METHODS

The 17-ketosteroids were determined with a technique according to Hamburger (1948) and the chemical analyses of oestrogens were performed with the method of Brown (1955) in a slightly modified form. Results with this method in a material of normal individuals have been reported elsewhere (Støa, 1956). During the first part of the investigation the oestrogens were also determined biologically. The assays were done with a technique according to that described by Pedersen-Bjergaard & Tønnesen (1948), which up to that time had been the ordinary routine method of our laboratory.

RESULTS

The results of the chemical oestrogen determinations performed before and during the first part of cortisone treatment are presented in Fig. 2. During the whole observation time the values were fluctuating within the normal range (Brown, 1955; Støa, 1956), and showed the usual characteristic cyclic variations. The values of oestradiol and oestrone were, however, relatively high. Considered as a whole, the excreted amounts of oestradiol and oestriol did not appear to be definitely influenced by the cortisone treatment. With regard to oestrone, however, a tendency towards decreasing values was observed after onset of treatment. The decrease was especially pronounced during the first part of the menstrual cycle, which is generally characterized by low, »basal« oestrogen values (Fig. 3). The average values of these first days of the cycle, before and after onset of treatment, were statistically shown to differ significantly (Table 1). Likewise, statistically a very probable decrease was found in the values of oestradiol and the biologically determined total oestrogens. As regards oestriol, no difference in the excretion could be shown.

In addition to the determinations here reported, a series of oestrogen analyses were done after cortisone treatment had been discontinued. Unfortunately, these determinations were performed only during the last part of the menstrual cycle. The average total values were slightly lower than the values found during the corresponding period before onset of treatment, but the difference was not significant.
Excretion of oestrogens before and during cortisone therapy in a 24-year old woman with hirsutism. The diagram shows the relation to cortisone dosage, menstruation and basal temperature.

CONCLUSIONS

In the present report of oestrogen determinations performed in a hirsute woman treated with cortisone, it could be shown, that controlled administration of cortisone did not interfere in any decisive degree with the normal cyclic variations in the oestrogenic activity of the ovaries. This finding is in good accordance with practical clinical experience (Greenblatt, 1953; Jones et al., 1953). Any general elevation of the amount of excreted oestrogens, as a possible result of a stimulated gonadotrophin production, was not observed. On the contrary, the values tended to decrease. The inhibition of oestrogen pro-
Fig. 3.
Excretion of oestrone during the first twenty days of the menstrual cycle. The fully drawn diagram represents the values before onset of cortisone treatment. The dotted diagram represents the values during cortisone treatment.

Table 1.
The effect of cortisone administration on the oestrogen excretion during the first twelve days of menstrual cycle. Oestrogens determined chemically as µg./day, and biologically as M. U./day.

<table>
<thead>
<tr>
<th>Oestrogenic substance</th>
<th>Before treatment</th>
<th>During treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Standard error of the mean</td>
<td>Average</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>14.9 ± 1.4</td>
<td></td>
<td>9.5 ± 1.3</td>
</tr>
<tr>
<td>Oestriol</td>
<td>4.8 ± 0.3</td>
<td></td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>Oestrone</td>
<td>11.3 ± 0.7</td>
<td></td>
<td>6.4 ± 0.5</td>
</tr>
<tr>
<td>Total oestrogens, biologically determined</td>
<td>126 ± 10</td>
<td></td>
<td>53 ± 15</td>
</tr>
</tbody>
</table>

213
duction is especially pronounced in the period of the cycle, when the ovarian oestrogenic activity is relatively low. This may indicate that a significant part of the oestrogens excreted in this postmenstrual period has its origin in the adrenal cortex, and that this part of the oestrogen production has been inhibited by cortisone therapy. At the present we are trying to reproduce these findings in other patients. We hope it may be possible in this way to throw light upon the mechanism of cortisone action in certain forms of menstrual irregularities and sterility.

**SUMMARY**

In a hirsute, regularly menstruating woman daily biological and chemical oestrogen determinations have been performed before and during cortisone therapy, as well as after the treatment had been concluded. The cortisone treatment did not interfere in any decisive degree with the cyclic variations in the oestrogenic activity of the ovaries. However, the excretion of oestrone and oestradiol, as well as the biologically determined urinary oestrogens were significantly lowered during the first period of the cycle, when the ovarian oestrogenic activity is relatively low. This may indicate that a significant part of the oestrogens excreted in this postmenstrual period has its origin in the adrenal cortex, and that this part of the oestrogen production has been inhibited.

**REFERENCES**