THYROID FUNCTION IN ORAL CONTRACEPTION

By

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ABSTRACT

Eighty one euthyroid, fertile women were treated cyclically with a daily dose of 5 mg of 6-methyl-6-dehydro-17\(\alpha\)-acetoxyprogesterone (megestrol acetate) + 0.1 mg of 17\(\alpha\)-ethynyl-oestradiol-3-methylether (mestranol) for an average of 16 months. During treatment a definite, but not significant, increase in protein-bound iodine (PBI) was found.

In 11 normal fertile women, the thyroid function was evaluated before, during, and after cyclical treatment with megestrol acetate + mestranol. The observation period was 4 to 19 months. The thyroidal 4-hour uptake and 24-hour uptake of \(^{131}\)I and the uptake of \(^{131}\)I-triiodothyronine (T\(_3\)) by erythrocytes and resin (Triosorb\(^*\)) were determined at short intervals. No significant changes were observed in the two first mentioned tests, but it was characteristic of all patients except one, that the red-cell uptake of T\(_3\) was significantly decreased to values below the lower limit of normal, within 1 to 2 months of the commencement of treatment, and that it then remained unchanged during the remainder of the treatment period. One month after treatment was discontinued, all patients except two showed values within normal limits. The uptake of T\(_3\) by resin showed similar patterns during the treatment period, but one month after the medication was withdrawn, only 2 out of the 9 patients had values within the normal range.

In 5 menopausal women, the thyroid function was evaluated before, during, and after continuous treatment with megestrol acetate by means of the same parameters as in the former group of patients. The observation period was 4 to 6 months. No significant changes were observed in the 4 indices of the thyroid function during and following treatment with mege-
strol acetate alone. It is therefore concluded that the significant decrease in the red-cell uptake and resin uptake of \( T_3 \) observed during treatment will megestrol acetate + mestranol is caused exclusively by the oestrogen in this combination.

During recent years combinations of orally active gestagens and oestrogens have achieved widespread acceptance for oral contraception and for the treatment of certain gynaecological disorders. Naturally, this has greatly stimulated interest in the effects of these compounds on the various endocrine glands. In recent years a number of reports of the effect on the thyroid function have been published. These studies have dealt with the concentration of protein-bound iodine (PBI) and thyroxine-binding globulin (TBG) in serum, the uptake of \( ^{131}I \) by the thyroid, and the uptake of \( ^{131}I \)-triiodothyronine (\( T_3 \)) by erythrocytes and resin.

It has been known for many years that the administration of oestrogens to euthyroid human subjects is associated with a marked increase in TBG and PBI (Alexander & Marmorston 1961; Dowling et al. 1956, 1959; Engbring & Engstrom 1959; Engstrom & Markardt 1954; Ingbar & Freinkel 1960; Mitchell & O’Rourke 1958; Robbins & Rall 1957; Sterling & Tabachnick 1961). The information available concerning the effect of oestrogens on the uptake of \( ^{131}I \) by the thyroid is controversial, but with regard to the uptake of \( T_3 \) by erythrocytes there is fairly good agreement. Clark & Horn (1965), Crispell et al. (1957), Dowling et al. (1960) and Hamolsky et al. (1959) all found a decrease in the red-cell uptake of \( T_3 \) during treatment with oestrogens.

Little is known of the effect of progesterone and gestagens alone on the thyroid function. Hollander et al. (1963) observed a significant increase in PBI and a decrease in the uptake of \( T_3 \) by erythrocytes during treatment with nor-ethynodrel, but no changes during treatment with medroxyprogesterone acetate. Winikoff & Taylor (1966) reported no changes in PBI and the red-cell uptake of \( T_3 \) during short-term treatment with ethynodiol diacetate.

During treatment with different combinations of oestrogens and gestagens Irizarry et al. (1966), Pincus (1964) and Winikoff & Taylor (1966) found no significant changes in the \( ^{131}I \) uptake by the thyroid. Fisher et al. (1966) observed a significant decrease in the resin uptake of \( T_3 \) during treatment with norethynodrel + mestranol. This finding was confirmed by Williams et al. (1966), who found the resin uptake of \( T_3 \) depressed and PBI elevated during treatment with the same steroids, whereas the thyroidal 24-hour uptake of \( ^{131}I \) and serum cholesterol were unchanged. Finally, Winikoff & Taylor (1966) observed a significant decrease in the resin uptake of \( T_3 \) during treatment with several different oral contraceptives. Many investigators (Florsheim & Faircloth 1964; Larsson-Cohn 1965; Pincus 1964; Roman & Bockner 1963) have reported a significant increase in PBI during oral contraception. In contrast to these in-
vestigators Walser et al. (1964) found no significant changes in PBI during treatment with norethisterone acetate + ethynyl-oestradiol.

The purpose of the present study was to evaluate the thyroid function during treatment with 6-methyl-6-dehydro-17α-acetoxyprogesterone (megestrol acetate) + 17α-ethynyl-oestradiol-3-methylether (mestranol) and megestrol acetate, respectively.

**MATERIALS AND METHODS**

Three groups of patients were studied. The first group consisted of 81 euthyroid, fertile women aged 18 to 32. They were all treated for contraceptive purposes and received a daily dose of 5 mg of megestrol acetate + 0.1 mg of mestranol cyclically from day 5 to day 24 of the cycle. The observation period for these patients was 12 to 21 months (with an average of 16 months). In all patients PBI was determined just before the treatment started and again at the end of the observation period.

The second group consisted of 11 euthyroid, fertile women aged 19 to 30. They were treated for contraceptive purposes and also received cyclical treatment with megestrol acetate + mestranol in the dose mentioned above. The observation period for this group was 4 to 19 months (with an average of 11 months). In all 11 patients the thyroid function was evaluated just before the treatment started, during the whole treatment period by determinations monthly or every second month, and finally one month after the withdrawal of medication. In all patients the thyroid function was assessed by determinations of the 4-hour uptake and the 24-hour uptake of $^{131}$I by the thyroid and the uptake of T₃ by erythrocytes. In addition, in 9 out of the 11 patients the uptake of T₃ by resin (Triosorb) was determined either during the whole observation period (6 patients) or only during a part of this period (3 patients).

The third group consisted of 5 menopausal women aged 46 to 51. They were treated because of climacteric complaints (hot flushes and sweating) and received a daily dose of 5 mg of megestrol acetate continuously. The observation period for this group was 4 to 6 months (with an average of 5 months). The thyroid function was determined before the treatment started, at monthly intervals during the treatment period, and one month after the medication was discontinued. In all patients the thyroid function was evaluated by determinations of the 4-hour uptake and the 24-hour uptake of $^{131}$I by the thyroid and the uptake of T₃ by erythrocytes. In 3 out of the 5 patients the uptake of T₃ by resin was also determined.

PBI was determined according to the method described by Barker (1948). The normal range of PBI was 3.0 μg/100 ml to 8.0 μg/100 ml.

The thyroidal 4-hour uptake and 24-hour uptake was determined after oral administration of 10 μc of $^{131}$I using the method of Friis & Christensen (1959). Before every new determination any possible residual activity was measured and subtracted from the result. The normal ranges of the thyroidal 4-hour uptake and 24-hour uptake were 15 to 45 per cent and 30 to 70 per cent of the administered dose, respectively, and the standard deviations ± 2.6 per cent and ± 3.8 per cent, respectively.

The uptake of T₃ by type O erythrocytes was determined using the method described by Hamolsky et al. (1957) and Friis (1960). The normal range of the red-cell uptake of T₃ was 6.0 to 10.5 per cent. The principle of this test is based on the competition for added T₃ between the binding sites of thyroid-binding serum proteins on the one hand, and a secondary binder, in this case the erythrocytes, on the other. The thyroid-
binding proteins in the \( a_1 \)- and \( a_2 \)-globulin fractions have greater affinity for thyroxine than triiodothyronine. If the thyroid function is decreased, less thyroxine will circulate and more binding sites will be available for the added \( T_3 \). The remaining \( T_3 \) will be bound by the erythrocytes, and this will result in a lower uptake by the erythrocytes.

Finally, the uptake of \( T_3 \) by an anion exchange resin-sponge (Triosorb) was determined according to the method of Mitchell et al. (1960). The principle of this test is the same as that of the red-cell uptake of \( T_3 \), but the resin-sponge offers some advantages over the erythrocytes. The greatest advantage is that the resin-sponge can be washed more quickly and more uniformly than the erythrocytes each time the test is performed. The normal range was 25 to 33 per cent.

**RESULTS**

In the first group of patients the values of PBI before treatment started, were within normal limits in all 81 patients, varying from 3.1 \( \mu g/100 \) ml to 8.2 \( \mu g/100 \) ml, with a mean value of 5.8 \( \mu g/100 \) ml. During treatment a definite, but not significant, increase in PBI was observed. The values during treatment ranged from 3.6 \( \mu g/100 \) ml to 11.8 \( \mu g/100 \) ml with a mean value of 7.2 \( \mu g/100 \) ml. There seemed to be no correlation between the increase in PBI and the length of the treatment period.

In the second group of patients, no significant changes were observed in the thyroidal 4-hour uptake and 24-hour uptake of \( {^1}^3^1^I \) during and after cyclical treatment with megestrol acetate + mestranol. The results are given as the mean value \( \pm \) standard deviation. The 4-hour uptake of \( {^1}^3^1^I \) was 34.9 \( \pm \) 11.9 per cent before treatment, 35.3 \( \pm \) 8.4 per cent during the treatment period, and 34.1 \( \pm \) 9.8 per cent one month after cessation of medication. The 24-hour uptake of \( {^1}^3^1^I \) was 59.1 \( \pm \) 17.0 per cent before treatment, 57.7 \( \pm \) 12.9 per cent during treatment, and 55.0 \( \pm \) 7.6 per cent after treatment. The red-cell uptake and resin uptake of \( T_3 \), however, showed characteristic changes during treatment, and therefore these results are analysed in more details.

It can be seen from Fig. 1 that the pre-treatment values of the red-cell uptake of \( T_3 \) were within normal limits in 10 out of the 11 patients. The last patient showed an increased red-cell uptake of \( T_3 \). It was characteristic of all patients except one, that the uptake of \( T_3 \) by erythrocytes was significantly decreased to values below the lower limit of normal within 1 to 2 months of the commencement of treatment, and remained almost unchanged during the remainder of the treatment period. After treatment was discontinued an increase in the red-cell uptake of \( T_3 \) was observed, and after 1 month all patients except two showed values within normal limits, but still below the pre-treatment levels.

Fig. 2 shows the uptake of \( T_3 \) by resin (Triosorb) before, during, and after treatment. Control values before the treatment started were obtained in only 6 out of the 9 patients studied. 5 out of these 6 patients showed values within
Red-cell uptake of $^{131}$-triiodothyronine (per cent)

Fig. 1.
Uptake of $T_3$ by erythrocytes in 11 fertile women during and following cyclical treatment with megestrol acetate + mestranol. Normal range 6.0 to 10.5 per cent. The mean values during treatment are connected by a heavy line. The stippled lines indicate the course after withdrawal of medication.

Resin uptake of $^{131}$-triiodothyronine (per cent)

Fig. 2.
Uptake of $T_3$ by resin (Triosorb) in 9 fertile women during and following cyclical treatment with megestrol acetate + mestranol. Normal range 25 to 35 per cent. For symbols see Fig. 1.

normal limits. The last patient had an increased uptake of $T_3$ by resin. It was characteristic of all 6 patients that the resin uptake of $T_3$ was already significantly decreased to values below the lower limit of normal during the first treatment-cycle. During the remainder of the treatment period, no further alterations in the resin uptake of $T_3$ were observed. One month after treatment was discontinued, only 2 out of the 9 patients showed values within normal
limits. In the other cases the resin uptake of T₃ was still lower than the pre-treatment levels.

In the third group of patients, no significant changes were found in the thyroidal uptake of ¹³¹I during and after continuous treatment with megestrol acetate alone. The results are given as the mean value ± standard deviation. The 4-hour uptake of ¹³¹I was 24.0 ± 5.4 per cent before treatment, 25.6 ± 5.0 per cent during treatment, and 26.8 ± 6.9 per cent after treatment. The 24-hour uptake of ¹³¹I was 37.7 ± 10.5 per cent before treatment, 42.9 ± 10.6 per cent during treatment, and 42.3 ± 7.9 per cent after treatment. The two other function tests showed small and opposite directed alterations during and after treatment. The red-cell uptake of T₃ was 6.4 ± 0.8 per cent before treatment, 7.3 ± 1.3 per cent during treatment, and 8.3 ± 0.8 per cent after treatment. The resin uptake of T₃ was 30.0 ± 2.8 per cent before treatment, 31.6 ± 2.1 per cent during treatment, and 27.3 ± 1.5 per cent after treatment.

**Discussion**

In the present study the thyroid function was evaluated during and after treatment with megestrol acetate + mestranol and megestrol acetate, respectively. For this purpose 4 thyroid function tests were selected, viz. the thyroidal 4-hour and 24-hour uptake of ¹³¹I and the uptake of T₃ by erythrocytes and resin. The two first mentioned tests give a measurement of the function of the thyroid gland, and the two last mentioned tests reflect the amount of free circulating thyroid hormone.

During treatment with megestrol acetate + mestranol a significant depression of the uptake of T₃ by erythrocytes and resin was observed 1 to 2 months after initiation of therapy, whereas the thyroidal 4-hour uptake and 24-hour uptake of ¹³¹I showed no significant alterations. After the first two treatment-cycles the values remained almost unchanged during the remainder of the treatment period. Our results indicate that megestrol acetate + mestranol have no direct effect on the thyroid gland, but cause an increase in the thyroid hormone-binding capacity of the serum proteins. These findings are in good agreement with the results reported by Fisher et al. (1966), Hollander et al. (1963), Irizarry et al. (1966), Pincus (1964), Williams et al. (1966) and Winikoff & Taylor (1966). Irizarry et al. (1966), Pincus (1964) and Williams et al. (1966) found no significant changes in the ¹³¹I uptake by the thyroid, and Fisher et al. (1966), Hollander et al. (1963), Williams et al. (1966) and Winikoff & Taylor (1966) observed a significant decrease in the uptake of T₃ by resin and erythrocytes during treatment with different oral contraceptives. They also found that the changes began 2 to 3 weeks after initiation of therapy, and this has been confirmed by the present investigation. The changes in red-cell uptake of
T₃ observed during treatment with megestrol acetate + mestranol seem to be reversible. One month after withdrawal of medication the red-cell uptake of T₃ had returned to normal values in 9 out of the 11 patients studied. At this time, however, the resin uptake of T₃ was normal in only 2 out of the 9 patients studied. This test thus appears to be more sensitive to the effect of these steroids. Unfortunately we had no opportunity of determining the red-cell uptake and resin uptake of T₃ later than one month after therapy had been discontinued, but our results are in fairly good agreement with the observations reported by Hollander et al. (1963), Williams et al. (1966) and Winikoff & Taylor (1966) who found a return to normal values of the red-cell uptake and resin uptake of T₃ 4 and 12 weeks after the withdrawal of therapy, respectively.

In contrast to the above mentioned results obtained during treatment with megestrol acetate + mestranol, we observed no significant changes in the thyroidal 4-hour uptake and 24-hour uptake of ¹³¹I and the uptake of T₃ by erythrocytes and resin during treatment with megestrol acetate alone. This confirms the finding reported by Hollander et al. (1963), who found no change in the red-cell uptake of T₃ during treatment with medroxyprogesterone acetate. The chemical constitution of this steroid is very similar to that of megestrol acetate. It is concluded that the changes observed during treatment with megestrol acetate + mestranol reflect exclusively the effect of the oestrogen on the thyroid hormone-binding capacity of the serum proteins.

**ACKNOWLEDGEMENTS**

This investigation has been supported by the Ford Foundation. Megestrol acetate and mestranol were supplied by courtesy of »Novo«, Copenhagen, Denmark.

**REFERENCES**


Received on February 20th, 1967.