

Effect of Cyclic Administration of Certain Progestin-Estrogen Combinations on the 24-Hour Radioiodine Thyroid Uptake

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ABSTRACT. The effects of short- and long-term administration of a mixture of progestogen and estrogen in different doses on the 24-hr radioiodine uptake by the thyroid gland were studied in a group of 154 women. EE3ME (ethinyl estradiol-3-methyl ether) was the estrogen used in all cases, while norethynodrel (17α -ethinyl-estra-5,10-ene-3-one) and ethynodioldiacetate (17α -ethinyl-4-estrene-3,17-diol-diacetate) were the progestogens. In all cases the compounds were administered daily, from the 5th through the 24th day of each cycle. The dosage schedule and duration of medication were as follows: Norethynodrel 5 mg and EE3ME 0.075 mg for 3 months in short-term users and for over 3 years in long-term users; norethynodrel 2.5

mg and EE3ME 0.1 mg after 3 years of use; ethynodioldiacetate 1 mg with EE3ME 0.1 mg and 2 mg with EE3ME 0.1 mg, both for 3 months. Statistical analysis of the results showed no significant difference between the average of the long-term users and those of the controls, or between the results of the tests before and after medication in the short-term users, with the exception of those taking ethynodioldiacetate 2 mg. The variation in this group, though significant by the *t* test, falls within the accepted day-to-day variation of radioiodine uptake and well within the limits of normal variation for euthyroid patients, so it is of no clinical importance. (*J Clin Endocr* 26: 6, 1966)

THE METABOLIC effects of estrogens on the binding capacity of human serum for thyroid hormone and the degradation fate of this substance have been the subject of numerous reports. The effect of estrogens on the iodide phase of thyroid function has not received great attention. There seems to be general agreement as to the increased thyroid hormone binding capacity of the

plasma proteins under the effect of exogenous estrogens (1-7), but the available information on the effect of estrogens, exogenous or endogenous, on the thyroid uptake is controversial. Dowling *et al.* (7) reported no effect on the thyroid uptake of euthyroid patients with the use of diethylstilbestrol, while Jensen (9) observed an increase of this function, and again Dowling *et al.* (10), studying the effects of endogenous estrogens in hydatidiform moles and in choriocarcinoma, found that the iodine uptake of the thyroid gland was elevated along with other parameters of thyroid function in three women with hydatidiform mole. Soliman and Reinecke (11) demonstrated increased uptake of ^{131}I in adrenalectomized rats under the influence of estrogen therapy, but no effect in intact animals.

The evidence obtained from experimental animals through deprivation of

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gonadal function indicates that the lack of sex hormones may affect the ^{131}I thyroid uptake either way. Information on this point is controversial, since Jovanovic *et al.* (12) reported a profound depression of thyroid uptake maximal three weeks after castration in either sex in the rat, while Tsuiguchi and Hatacke (13) found increased uptake maximal at 48 hours post ovariectomy in adult white rats. Becchini and Bianchi (14) reported increased thyroid ^{131}I uptake by the administration of estrogens to rats, similar to that obtained with TSH, but the effect was canceled out by the simultaneous administration of the two drugs.

The influence of exogenous stimulation with female sex hormones assayed by histologic studies of the thyroid tissue shows unequivocally an opposing effect of estrogens and progestogens on the glandular epithelium. Barbazza *et al.* (15) concluded that estrogens block the process of regeneration of epithelium in partially thyroidectomized rats, but, on the contrary, Welch and collaborators (16) describe stimulation of epithelial growth (hypertrophy) similar to that of pregnancy in virgin rats treated with progesterone. The effect of progesterone on the ^{131}I thyroid uptake was measured in intact male rats by Andreoli (17), who found a depressing effect of this hormone on the iodine accumulation and renal iodine clearance. A similar result was found in adrenalectomized rats. The effect of anticonceptive therapy with combined estrogen-progestin type of medication at short or long intervals on the 24-hour radioiodine uptake by the thyroid gland in humans is not known. This study intends to evaluate this problem.

Materials and Methods

Selection of patients and sample design. Participants in this study were Puerto Rican women from the Puerto Rico Family Plan-

ning Association representing a sample selected from the lower socioeconomic strata of the general population. The sample consisted of nonmedicated women to be examined before and after 3 months of therapy; a group medicated for over 3 years to be examined twice within a 3-month interval, and a control group to be examined twice in 3 months.

The sample design is as follows:

Group I. Participants examined before and after at least 3 months of cyclic administration of 5 mg Enovid (17 α -ethinylestra-5,10-eneolone plus 0.075 mg of ethinyl estradiol-3-methyl ether).
Group II. Participants examined before and after at least 3 months' administration of 1 mg of Ovulen (17 α -ethinyl-4-estrene-3,17-diol-diacetate plus 0.1 mg of ethinyl-estradiol-3-methyl ether).

Group II-B. Participants examined before and after 3 months' administration of 2 mg Ovulen.

Group III-A. Participants under continuous cyclic administration of 5 mg Enovid for 3 yr examined twice in 3 months.

Group III-B. Participants under continuous cyclic administration of 2.5 mg of Enovid for 3 yr examined twice in 3 months.

Group IV. Participants not taking anticonceptive substances but who employed vaginal contraceptive devices.

All participants were taking their medication in cyclic form, starting the fifth day of the cycle and taking it daily for 20 consecutive days, waiting for withdrawal bleeding and re-starting on the fifth day of the following cycle. When withdrawal bleeding did not occur the subject would re-start medication 8 days after her last pill. Groups I, II-A, II-B and III-A and III-B were compared with group IV, but in addition subgroups III-A and III-B were considered as medicated controls at 2 dosage levels, while group IV represented the nonmedicated control. Both medicated and nonmedicated controls served to monitor the magnitude of freely occurring spontaneous physiologic variations during the 3 months' interval of the study.

Procedures. Participants were instructed to come to the laboratory in the fasting state. A dose of 20–50 μC of iodine-131 was administered early in the morning of the day prior

TABLE 1. Distribution and characteristics of 154 participants by group

Group	Avg age	Avg no. pregnancies (fertility)	Education	Per capita weekly income U. S. dollars	No. participants
I	30	4.6	8.8	9.8	28
II-A	23	3.1	8.3	7.7	13
II-B	21	2.5	8.8	7.9	26
III-A	31	5.3	—	—	25
III-B	25	3.0	—	—	32
IV	31	5.5	6.6	6.0	30

to the uptake measurement. The technique is the usual 24-hr radioiodine uptake according to the method introduced by Brucer (18) with the following modifications: standard measurements are done in a plastic phantom using iodine-131 capsules as sources instead of mock iodine.

In our experience this technique shows a very low intra-individual variation (standard deviation) of 0.75 units of uptake, a working error of less than 5% of the measurement. Radioiodine thyroid uptake was determined twice within a period of at least 3 months in all patients in the 4 groups.

Results

One hundred fifty-four healthy participants with no evidence of thyroid disease were selected for this study. The socioeconomic characterization of the participants in the different groups showed an average age that varied from 21 to 30 years, average number of pregnancies two to five; average education sixth to ninth grade; and average per

TABLE 2. Comparison of average thyroïdal uptake before and after drug intake

Group	I	II-A	II-B
No. of subjects	28	13	26
Avg before drug	19.5 (± 6.7)	20.6 (± 3.7)	18.1 (± 5.1)
Avg after drug	17.2 (± 5.9)	18.3 (± 3.9)	16.6 (± 4.0)

Standard deviation in parentheses.

Statistical test performed: *t* test for significance of difference between means before and after drug intake, for each group. Group II-B: significant difference at 5% level.

capita weekly income of six to ten dollars (Table 1).

The results of the 24-hour radioiodine uptake in 28 participants of group I and of 39 in group II, before and after medication, are shown in Table 2. The average percentage of thyroid uptake before medication was 18.9 (group I), 20.6 (group II-A) and 18.1 (group II-B), and after three months' medication the average per cent uptake was 17.5 (group I), 18.3 (group II-A) and 16.6 (group II-B). Differences in uptakes for group I and subgroup II-A were not significant to the *t* test. The difference in subgroup II-B is statistically significant to the *t* test at the 5% level.

Twenty-five long-term users of 5 mg Enovid had an average per cent uptake of 18.2 and 17.5 three months apart; while 32 long-term users of 2.5 mg

TABLE 3. Comparison of average thyroïdal uptake in long-term users and control groups, at the beginning of the study and three months after

Group	III-A	III-B	Control
No. of subjects	25	32	30
Base-line avg uptake	18.2 (± 6.3)	21.4 (± 9.6)	21.4 (± 4.8)
Avg uptake 3 months after	17.5 (± 4.9)	21.7 (± 10.2)	20.2 (± 4.6)

Statistical test performed: *t* test for significance of difference between means of each group vs. control group. No significant difference at 5% level.

Enovid had 21.4 and 21.7 average per cent uptake in the same period. The control group showed 21.4 and 20.2 average per cent uptake in three months.

The differences in the means of the uptakes between subgroups III-A, III-B and the control are not statistically significant at the 5% level (Table 3).

The magnitude of the freely occurring spontaneous physiologic variation at the three-month interval was of the order of 4 units of uptake for the medicated (long-term users) groups III-A and III-B and for the control group IV (graphs 1, 2, 3 in Fig. 1).

Discussion

The data obtained uniformly appear to indicate no measurable significant change in the radioiodine thyroid uptake function in these groups of patients using Enovid or Ovulen on two different dosage schedules over a relatively short period of time (3 months).

Similarly, no appreciable or significant effect was seen on long-term users of Enovid when compared with the control group. The difference in the radioiodine uptake before and after three months of anticonceptive treatment in participants of subgroup II-B, though statistically significant, is within the expected range of normal physiologic variation. The normal expected day-to-day variation has been reported to be plus or minus seven units of uptake in normal euthyroid individuals (19), and in a few instances it may even be over plus or minus ten units of uptake. Our patients were examined three months later and the degree of variation (average deviation) was of the order of ± 4 units of uptake for the control groups of medicated and nonmedicated patients (graphs 1, 2, 3 in Fig. 1). The average deviation for subgroup II-B was 4.8 units.

An incidental finding in this study is

the observation of a low average value for the 24-hour radioiodine uptake tests in all the groups studied: lowest 16.6%; highest 21.7%. This is remarkable when compared with the average uptake of the order of 25% for euthyroid patients from clinical populations in Puerto Rico

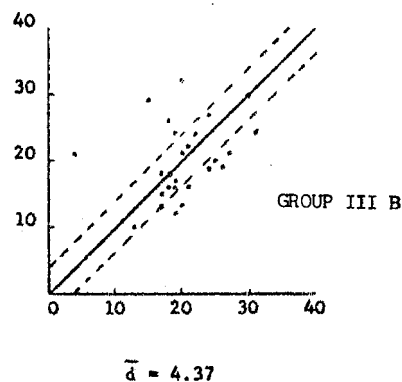
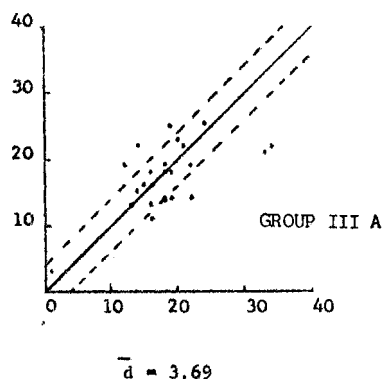
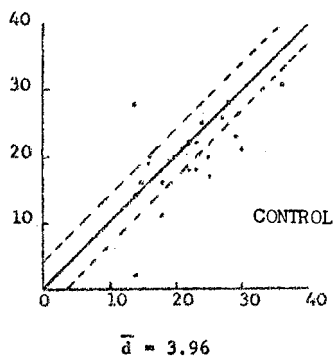


FIG. 1. Average intra-individual variation at 3-month interval of control and long-term users.

(20; and personal communication from Roberto Busó). No explanation can be offered at this time for this difference, and additional investigations will be necessary to elucidate this problem.

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