

INCREASED NEED FOR THYROXINE IN WOMEN WITH HYPOTHYROIDISM DURING ESTROGEN THERAPY

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ABSTRACT

Background Women with hypothyroidism that is being treated with thyroxine often need higher doses when they are pregnant. Whether this need can be attributed solely to estrogen-induced increases in serum thyroxine-binding globulin or whether other factors are involved is not known.

Methods In 11 postmenopausal women with normal thyroid function and 25 postmenopausal women with hypothyroidism treated with thyroxine, I assessed thyroid function before they started estrogen therapy and every 6 weeks for 48 weeks thereafter. The women with hypothyroidism included 18 women receiving thyroxine-replacement therapy and 7 women receiving thyrotropin-suppressive thyroxine therapy. On each occasion, serum thyroxine, free thyroxine, thyrotropin, and thyroxine-binding globulin were measured.

Results In the women with normal thyroid function, the serum free thyroxine and thyrotropin concentrations did not change, whereas at 12 weeks the mean (\pm SD) serum thyroxine concentration had increased from $8.0 \pm 0.9 \mu\text{g}$ per deciliter ($103 \pm 12 \text{ nmol}$ per liter) to $10.4 \pm 1.5 \mu\text{g}$ per deciliter ($134 \pm 19 \text{ nmol}$ per liter, $P < 0.001$) and the serum thyroxine-binding globulin concentration had increased from $20.3 \pm 3.5 \text{ mg}$ per liter to $31.3 \pm 3.2 \text{ mg}$ per liter ($P < 0.001$). The women with hypothyroidism had similar increases in serum thyroxine and thyroxine-binding globulin concentrations during estrogen therapy, but their serum free thyroxine concentration decreased from $1.7 \pm 0.4 \text{ ng}$ per deciliter ($22 \pm 5 \text{ pmol}$ per liter) to $1.4 \pm 0.3 \text{ ng}$ per deciliter ($18 \pm 4 \text{ pmol}$ per liter, $P < 0.001$) and their serum thyrotropin concentration increased from 0.9 ± 1.1 to $3.2 \pm 3.1 \mu\text{U}$ per milliliter ($P < 0.001$). The serum thyrotropin concentrations increased to more than $7 \mu\text{U}$ per milliliter in 7 of the 18 women in the thyroxine-replacement group and to more than $1 \mu\text{U}$ per milliliter in 3 of the 7 women in the thyrotropin-suppression group.

Conclusions In women with hypothyroidism treated with thyroxine, estrogen therapy may increase the need for thyroxine. (N Engl J Med 2001;344:1743-9.)

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WOMEN with hypothyroidism need an average of 45 percent more thyroxine during pregnancy to maintain euthyroidism.¹⁻⁵ The possible causes of this increased need include an increase in serum thyroxine-binding globulin concentrations, degradation of thyroid hormone by the placenta, transfer of thyroxine from mother to fetus, and increased maternal clearance of thyroxine.¹⁻⁶ Any of these factors would lead to a

decrease in the serum free thyroxine concentration. In women with normal thyroid function,⁶ thyroxine secretion can increase to compensate for a decrease in the serum free thyroxine concentration, but it cannot increase in women with hypothyroidism.

Among the factors that may affect the need for thyroxine in pregnant women, only the increase in the serum thyroxine-binding globulin concentration is induced by estrogen. The administration of estrogen causes dose-dependent increases in the serum concentrations of thyroxine-binding globulin and thyroxine in women with normal thyroid function,^{6,7} but its effects in women with hypothyroidism are not known. I undertook this study to determine the effects of the administration of estrogen on pituitary-thyroid function in normal women and in women receiving thyroxine therapy for chronic hypothyroidism.

METHODS**Study Subjects**

Postmenopausal women who had indications for estrogen therapy and who agreed to take estrogen were asked to participate in the study. The indications for estrogen therapy included hot flashes, excessive sweating, and the treatment or prevention of osteoporosis. A total of 36 women were recruited: 11 women with normal thyroid function and no known medical problems and 25 women with primary hypothyroidism diagnosed between 18 and 68 months earlier (mean [\pm SD], 47 ± 9 months) who had received the same doses of thyroxine for more than 9 months. Of these 25 women, 18 were receiving thyroxine-replacement therapy for hypothyroidism caused by chronic autoimmune thyroiditis (in 10 women), previous radioactive iodine therapy (in 4 women), or total thyroidectomy (in 4 women). The remaining seven women had previously undergone thyroidectomy and radioactive iodine treatment for thyroid cancer and were receiving thyrotropin-suppressive thyroxine therapy. These two groups are referred to here as the thyroxine-replacement group and the thyrotropin-suppression group, respectively. The study was approved by the institutional review board, and all the women gave written informed consent.

Study Protocol

Estrogen therapy was initiated after a clinical evaluation that included a physical examination and mammography. All the women received conjugated estrogens in a daily oral dose of 0.625 mg, and women who had not undergone hysterectomy also received medroxyprogesterone acetate in a dose of 5 mg per day for 12 days of each month. After 12 weeks of treatment, the dose of conjugated estrogens was decreased to 0.3 mg per day in one woman because of breast tenderness; the dose was increased to 1.25 mg daily in another woman because of persistent menopausal symptoms. For

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these two women, only the data obtained before the dose was changed were included in the analysis. The women had follow-up visits every 6 weeks for 48 weeks. At each visit, thyroid function was assessed clinically, and serum thyroxine, the thyroid hormone-binding index, free thyroxine, thyrotropin, and thyroxine-binding globulin were measured. Serum thyroglobulin was measured every 12 weeks in the women in the thyrotropin-suppression group. The clinical assessment included a focused history taking and a physical examination pertinent to thyroid dysfunction.

The women who were being treated with thyroxine continued to take the same brand and dose of thyroxine they had been taking before the study. The dose was increased in the women in the thyroxine-replacement group if the serum thyrotropin concentration increased to more than 7 μU per milliliter. The dose was increased in the women in the thyrotropin-suppression group if the serum thyrotropin concentration increased to more than 1 μU per milliliter. Data obtained after the dose of thyroxine was increased were not included in the analysis. At the end of the 48-week study period, all samples from each woman were reanalyzed with a single assay, and these results were used in the statistical analyses.

Laboratory Methods

Serum thyroxine and the thyroid hormone-binding index were measured with the use of kits from Abbott Laboratories (Abbott Park, Ill.). The serum free thyroxine index was calculated as the product of the serum thyroxine concentration and the thyroid hormone-binding index value. Serum free thyroxine was measured by a two-step radioimmunoassay with the use of kits from DiaSorin (Stillwater, Minn.). Serum thyrotropin was measured by fluorimmunoassay with the use of kits from Wallac Oy (Turku, Finland). The lower limit of detectability with the assay was 0.002 μU per milliliter, and the normal range was 0.5 to 5.0 μU per milliliter. Serum thyroxine-binding globulin and thyroglobulin were measured by radioimmunoassay at Nichols Laboratories (San Juan Capistrano,

Calif.). All other measurements (of thyroxine, thyrotropin, the thyroid hormone-binding index, and free thyroxine) were performed at the University Hospitals of Cleveland. The intraassay coefficients of variation of these assays varied from 1.2 percent to 3.5 percent.

Statistical Analysis

The pretreatment characteristics of the women with hypothyroidism and the women with normal thyroid function were compared by means of unpaired t-tests. Within each group and subgroup, the data obtained both before the administration of estrogen and after 12, 24, and 48 weeks of estrogen therapy were analyzed by repeated-measures analysis of variance and two-sided t-tests. The results for the women who received medroxyprogesterone were first analyzed separately from the results for those who did not. Because medroxyprogesterone had no effect on thyroid function, the results were then combined.

RESULTS

The ages and weights of the women with hypothyroidism and the women with normal thyroid function were similar (Table 1). The 7 women in the thyrotropin-suppression group were taking higher daily doses of thyroxine than the 18 women in the thyroxine-replacement group. At base line, all the women had high serum gonadotropin concentrations and low serum estradiol concentrations, findings consistent with their postmenopausal state (data not shown).

All but five women completed the study. Serious medical illnesses requiring the discontinuation of estrogen developed in two of these women: pulmonary embolus in one woman with normal thyroid function,

TABLE 1. BASE-LINE CHARACTERISTICS AND RESULTS OF THYROID-FUNCTION TESTS IN THE WOMEN WITH NORMAL THYROID FUNCTION AND THE WOMEN WITH HYPOTHYROIDISM.*

VARIABLE	WOMEN WITH NORMAL THYROID FUNCTION (N=11)	ALL WOMEN WITH HYPOTHYROIDISM (N=25)	THYROXINE-REPLACEMENT GROUP (N=18)	THYROTROPIN-SUPPRESSION GROUP (N=7)
Age (yr)	53±10	49±10	52±7	40±11†
Weight (kg)	70.0±7.7	75.0±15.0	77.3±16.0	68.6±11.0
Treatment with progestin (no.)	6	15	11	4
Duration of hypothyroidism (mo)	NA	47±9	49±8	42±10
Dose of thyroxine ($\mu\text{g}/\text{day}$)	NA	114±34	104±33	138±20‡
Serum thyroxine concentration ($\mu\text{g}/\text{dl}$)	8.0±0.9	9.2±1.7	8.3±1.0	11.0±1.0§
Thyroid hormone-binding index	0.9±0.1	1.0±0.03	1.0±0.1	1.0±0.1
Serum free thyroxine index	7.3±1.1	9.2±1.9	8.2±1.0¶	11.3±1.4
Serum free thyroxine concentration (ng/dl)	1.2±0.2	1.7±0.4	1.5±0.3	2.1±0.3§
Serum thyrotropin concentration ($\mu\text{U}/\text{ml}$)	1.3±0.6	0.9±1.1	1.1±1.6	0.1±0.1§
Serum thyroxine-binding globulin concentration (mg/liter)	20.3±3.5	20.8±3.1	20.8±2.9	20.7±3.0

*Plus-minus values are means ±SD. To convert serum thyroxine values to nanomoles per liter and serum free thyroxine values to picomoles per liter, multiply by 12.87. NA denotes not applicable.

†P=0.05 for the comparison with the women in the thyroxine-replacement group.

‡P=0.007 for the comparison with the women in the thyroxine-replacement group.

§P<0.001 and P=0.009 for the comparisons with the women with normal thyroid function and with those in the thyroxine-replacement group, respectively.

¶P=0.02 for the comparison with the women with normal thyroid function.

||P<0.001 for the comparisons with both women with normal thyroid function and those in the thyroxine-replacement group.

at six months, and breast cancer in one woman with hypothyroidism, at nine months. Three additional women elected to discontinue estrogen therapy after six to nine months for personal reasons. The data for these five women up to the time they discontinued estrogen therapy were included in the analysis.

Thyroid Function at Base Line

As compared with the women with normal thyroid function, the women in the thyroxine-replacement group had similar serum concentrations of thyrotropin and thyroxine but higher serum free thyroxine index values and serum free thyroxine concentrations (Table 1). The women in the thyrotropin-suppression group had lower serum thyrotropin concentrations and higher serum thyroxine concentrations, serum free thyroxine concentrations, and serum free thyroxine index values than the women with normal thyroid

function (Table 1). The differences reflected the higher doses of thyroxine given to the women in the thyrotropin-suppression group. The serum thyroxine-binding globulin concentrations were similar in all three groups.

Thyroid Function during Estrogen Therapy in the Women with Normal Thyroid Function

In the women with normal thyroid function, estrogen therapy for 6 weeks resulted in a significant increase in the mean (\pm SD) serum concentrations of thyroxine and thyroxine-binding globulin, and the values were slightly higher at 12 weeks (serum thyroxine, $10.4 \pm 1.5 \mu\text{g}$ per deciliter [$134 \pm 19 \text{ nmol}$ per liter]; serum thyroxine-binding globulin $31.3 \pm 3.2 \text{ mg}$ per liter; $P < 0.001$ for both comparisons with the baseline values), after which the values did not change materially (Fig. 1). The mean maximal increase in the se-

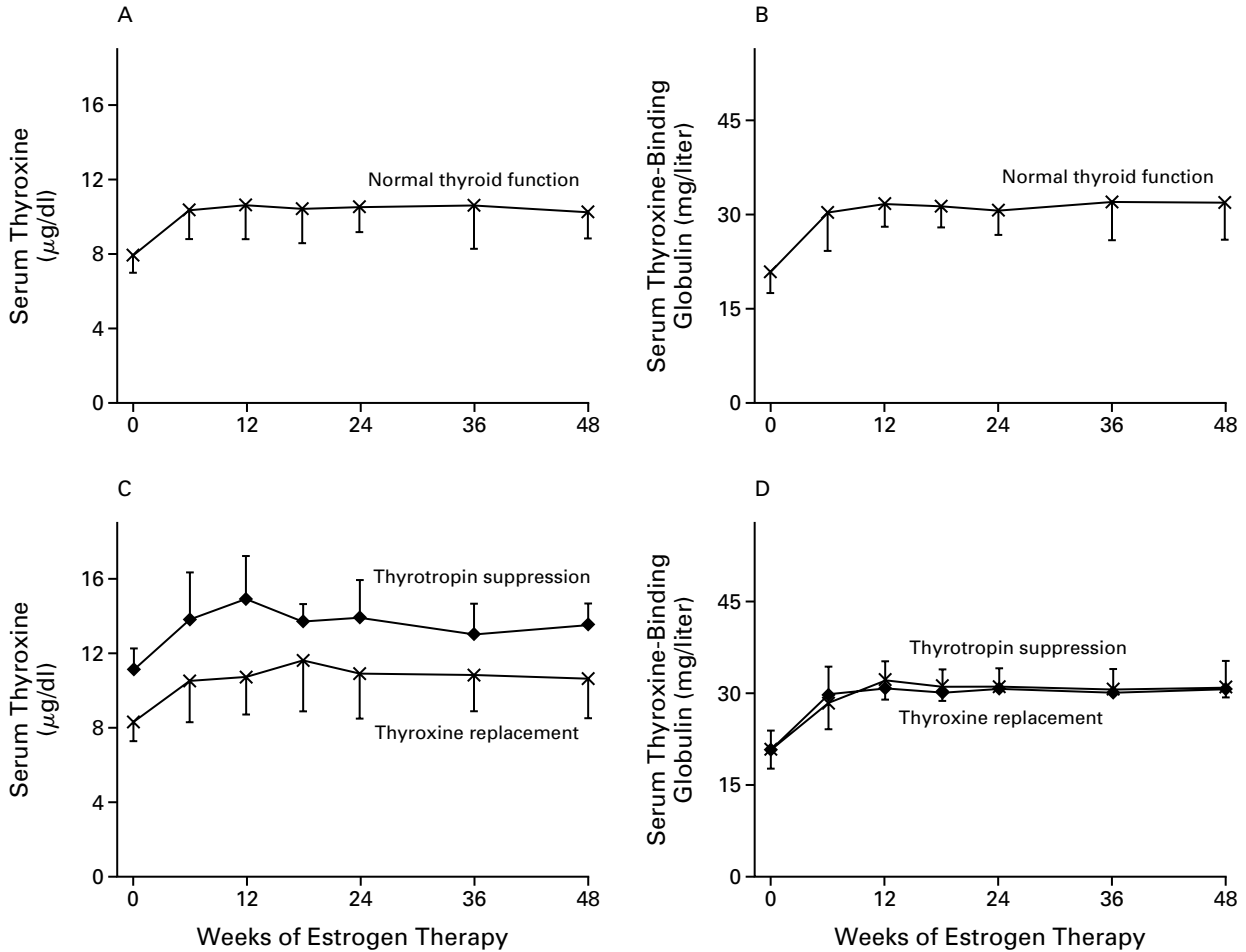


Figure 1. Mean (\pm SD) Serum Concentrations of Thyroxine (Panels A and C) and Thyroxine-Binding Globulin (Panels B and D) in 11 Women with Normal Thyroid Function, 18 Women with Hypothyroidism in the Thyroxine-Replacement Group, and 7 Women with Hypothyroidism in the Thyrotropin-Suppression Group, All of Whom Received Estrogen Therapy for 48 Weeks. The increases in serum thyroxine and thyroxine-binding globulin concentrations at approximately 12 weeks (to levels that were maintained thereafter) were significant ($P < 0.001$) in all groups.

rum thyroxine concentration was $2.4 \pm 1.0 \mu\text{g}$ per deciliter ($31 \pm 13 \text{ nmol}$ per liter). The increase in the serum thyroxine-binding globulin concentration was accompanied by a decrease in the thyroid hormone-binding index value (to a mean of 0.7 ± 0.1 at 12 weeks, $P < 0.001$). The serum free thyroxine index values did not change significantly (data not shown), nor did the serum free thyroxine or thyrotropin concentrations (Fig. 2).

Thyroid Function during Estrogen Therapy in the Women with Hypothyroidism

The serum thyroxine-binding globulin concentrations increased at six weeks in response to estrogen therapy in the women with hypothyroidism that was being treated with thyroxine. The values reached a

peak at 12 weeks ($30.8 \pm 4.0 \text{ mg}$ per liter, $P < 0.001$) (Fig. 1), after which they did not change substantially. The serum thyroxine concentrations increased in a parallel manner in these women. The 12-week values were $10.9 \pm 2.3 \mu\text{g}$ per deciliter ($140 \pm 30 \text{ nmol}$ per liter) for women in the thyroxine-replacement group and $14.5 \pm 1.2 \mu\text{g}$ per deciliter ($187 \pm 15 \text{ nmol}$ per liter) for women in the thyrotropin-suppression group ($P < 0.001$ for the comparisons with base-line values in both groups). The mean maximal increase in the serum thyroxine concentration was $2.5 \pm 1.0 \mu\text{g}$ per deciliter ($32 \pm 13 \text{ nmol}$ per liter) among the women in the thyroxine-replacement group and $3.3 \pm 0.8 \mu\text{g}$ per deciliter ($42 \pm 10 \text{ nmol}$ per liter) among the women in the thyrotropin-suppression group ($P = 1.00$ and $P = 0.04$, respectively, for the comparisons with the women with

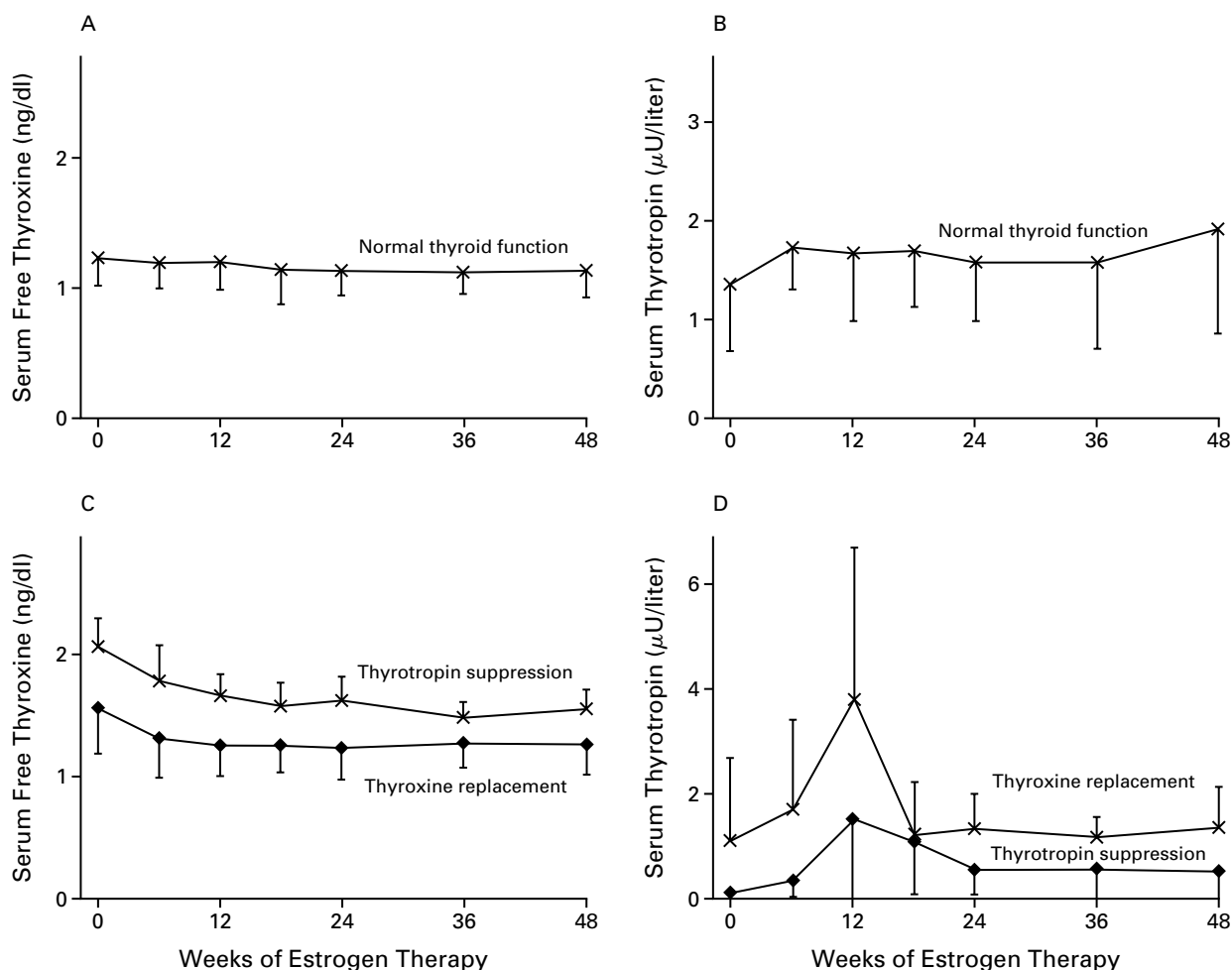


Figure 2. Mean (\pm SD) Serum Concentrations of Free Thyroxine (Panels A and C) and Thyrotropin (Panels B and D) in 11 Women with Normal Thyroid Function, 18 Women with Hypothyroidism in the Thyroxine-Replacement Group, and 7 Women with Hypothyroidism in the Thyrotropin-Suppression Group, All of Whom Received Estrogen Therapy for 48 Weeks.

The serum free thyroxine and thyrotropin concentrations did not change in the women with normal thyroid function, but the serum free thyroxine concentrations decreased and the serum thyrotropin concentrations increased in both groups of women with hypothyroidism.

normal thyroid function). The thyroid hormone-binding index value in the women with hypothyroidism decreased to 0.8 ± 0.1 ($P < 0.01$ for the comparison with base line). The serum free thyroxine index values did not change in response to estrogen therapy.

In contrast to the stable level in the women with normal thyroid function, the serum free thyroxine concentration had decreased at 12 weeks in the women with hypothyroidism from 1.7 ± 0.4 ng per deciliter (22 ± 5 pmol per liter) to 1.4 ± 0.3 ng per deciliter (18 ± 4 pmol per liter, $P < 0.001$). These concentrations had decreased at 12 weeks from 1.5 ± 0.3 ng per deciliter (19 ± 4 pmol per liter) to 1.2 ± 0.3 ng per deciliter (15 ± 4 pmol per liter, $P = 0.01$) in the women in the thyroxine-replacement group and from 2.1 ± 0.3 ng per deciliter (27 ± 4 pmol per liter) to 1.7 ± 0.2 ng per deciliter (22 ± 3 pmol per liter, $P = 0.01$) in the women in the thyrotropin-suppression group. The serum free thyroxine concentration remained lower than the baseline concentration throughout the study (Fig. 2). This

decrease was accompanied by a significant increase in the serum thyrotropin concentration in both subgroups ($P = 0.03$ and $P = 0.05$, respectively) at 12 weeks (Fig. 2 and 3). The decrease in the serum free thyroxine concentration correlated inversely with the increase in the serum thyrotropin concentration in the women in the thyroxine-replacement group ($r = 0.68$, $P < 0.001$) and that in the thyrotropin-suppression group ($r = 0.66$, $P = 0.04$).

The changes in the serum thyrotropin concentrations shown in Figure 3 were clinically important in 10 of the 25 women with hypothyroidism. Specifically, seven women in the thyroxine-replacement group had increases in the serum thyrotropin concentration to more than $7 \mu\text{U}$ per milliliter, and their dose of thyroxine was therefore increased. Only one of these seven women had any symptoms or signs of hypothyroidism. None of the women whose serum thyrotropin concentrations remained lower than $7 \mu\text{U}$ per milliliter had symptoms of hypothyroidism. The serum thy-

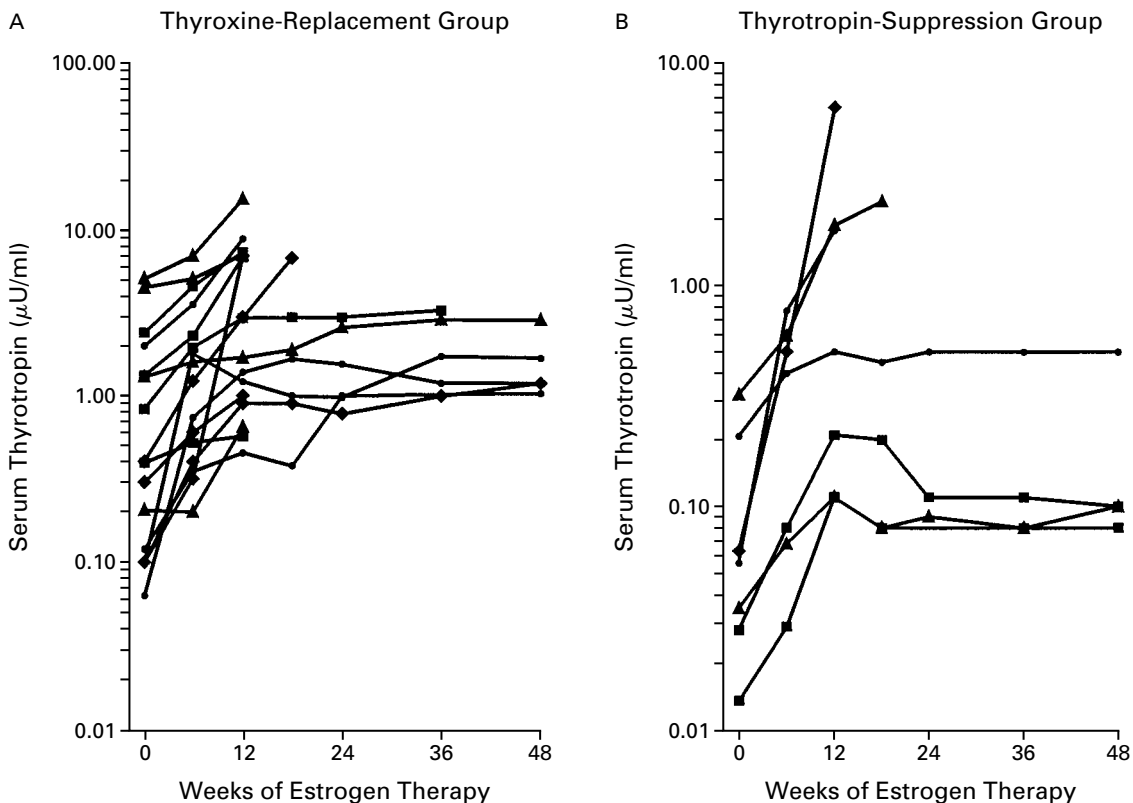


Figure 3. Serial Measurements of Serum Thyrotropin in 18 Women with Hypothyroidism in the Thyroxine-Replacement Group (Panel A) and 7 Women with Hypothyroidism in the Thyrotropin-Suppression Group (Panel B), All of Whom Received Estrogen Therapy for 48 Weeks.

Each point represents a determination in an individual woman. By the 12th week of estrogen therapy, 7 of the 18 women in the thyroxine-replacement group had serum thyrotropin concentrations of more than $7 \mu\text{U}$ per milliliter, and 3 of the 7 women in the thyrotropin-suppression group had serum thyrotropin concentrations of more than $1.0 \mu\text{U}$ per milliliter. The doses of thyroxine were then increased in these 10 women; the data collected thereafter are not shown. The scales on the y axes of Panels A and B differ.

rotropin concentrations increased to more than 1 μU per milliliter in three women in the thyrotropin-suppression group; none had clinical manifestations of hypothyroidism. However, two of these three women also had increases in the serum thyroglobulin concentration from undetectable values (less than 0.5 ng per milliliter) to 2.5 ng per milliliter and 6 ng per milliliter, respectively. The doses of thyroxine in these three women had to be increased by 25 to 50 μg per day to achieve thyrotropin suppression similar to pretreatment values.

DISCUSSION

This study demonstrates that women with hypothyroidism that is being treated with thyroxine who then receive estrogen have alterations in serum free thyroxine and thyrotropin concentrations that are small but potentially clinically important. In contrast, the serum concentrations of free thyroxine and thyrotropin did not change in the women with normal thyroid function. The increase in the serum thyrotropin concentrations in the women in the thyroxine-replacement group might have resulted in symptoms of hypothyroidism had their doses not been increased. Similarly, an increase in the serum thyrotropin concentration could potentially be harmful in women receiving thyrotropin-suppressive thyroxine therapy for thyroid cancer.

The uniformity of the changes in the serum concentrations of free thyroxine and thyrotropin indicates that noncompliance with thyroxine therapy is an unlikely explanation for the reported alterations. Furthermore, because of the chronic nature of the deficiency of thyroid hormone in the women, it is unlikely that these alterations reflect a decrease in residual functioning thyroid tissue.

The alterations in the serum concentrations of free thyroxine and thyrotropin in the women with hypothyroidism most likely resulted from estrogen-induced increases in the serum thyroxine-binding globulin concentration. This increase in binding would be expected to slow the entry of thyroxine into cells, including pituitary cells, thereby reducing thyroid hormone action in tissue. Alternatively, estrogen might lower the serum free thyroxine concentration by increasing the clearance of thyroxine. However, that would be expected to lower the serum concentrations of both thyroxine and free thyroxine. In fact, in subjects with normal thyroid function, estrogen therapy is known to slow the fractional daily clearance of thyroxine but not to alter the total daily clearance.⁸ The reported clinical and biochemical improvement during the administration of estrogen in women with hyperthyroidism caused by Graves' disease and those with thyrotoxicosis facticia^{8,9} accords with the results of the current study.

Pregnant women with hypothyroidism who are treated with thyroxine require an average increase of

45 percent in the dose of thyroxine to maintain euthyroidism.^{1,3,5} In this study, only a minority of the women with hypothyroidism had increases in their serum thyrotropin concentrations that were sufficient to warrant an increase in the dose of thyroxine. However, the increases in the serum concentrations of thyroxine and thyroxine-binding globulin that occur during pregnancy⁷ in women with normal thyroid function are similar to those that occur during estrogen therapy. Thus, it is likely that hyperestrogenemia does not mediate all of the alterations that occur in pregnant women. It is unlikely that changes in another transport protein for thyroxine, transthyretin, contribute to the alterations, since the serum transthyretin concentration does not change during pregnancy.⁷

Estrogen raises the serum thyroxine-binding globulin concentration by increasing sialylation of the protein, which slows its clearance,¹⁰ and also by enhancing its biosynthesis.¹¹ Conversely, androgens decrease the serum thyroxine-binding globulin concentration and therefore decrease the serum thyroxine concentration.¹² In women with hypothyroidism treated with thyroxine who are given an androgen, the serum free thyroxine concentration sometimes increases sufficiently to cause clinical manifestations of hyperthyroidism.¹²

In summary, women with no thyroid disease adapt quickly to estrogen-induced increases in the serum thyroxine-binding globulin concentration. In contrast, women with hypothyroidism who are treated with estrogen have a decrease in the serum free thyroxine concentration sufficient to increase the serum thyrotropin concentration, resulting in an increased need for thyroxine. Thus, serum thyrotropin should be measured approximately 12 weeks after estrogen therapy is initiated in women with hypothyroidism, especially in those with thyroid cancer who are being treated with thyroxine to achieve thyrotropin suppression.

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