# Hypothyroid Women Need More Thyroxine When Pregnant

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*Background.* There have been several published reports that hypothyroid women do not need to increase the dose of levothyroxine when they become pregnant.

*Methods.* For this study, 20 pregnant women who were hypothyroid as a result of surgical thyroidectomy, radioiodine therapy, or combination therapy were followed for the duration of their pregnancies. These patients were seen regularly, and evaluated clinically and by measurement of free thyroxine ($FT_4$) and thyrotropin (thyroid-stimulating hormone [TSH]).

*Results.* The amount of levothyroxine that was adequate in the nonpregnant state was found to be inadequate during pregnancy. The dosage of levothyroxine given to these patients was increased by an average of 36 μg and returned to earlier levels after delivery. There was considerable individual variation in the requirement for additional levothyroxine during pregnancy.

*Conclusions.* For hypothyroid pregnant patients, thyroid function tests, especially TSH, are recommended during each trimester to determine the need for additional levothyroxine.

*Key words.* Hypothyroidism; pregnancy; levothyroxine, thyrotropin.
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Thyroid diseases such as thyroid cancers,[1] thyroid nodules, and Graves' hyperthyroidism are significantly more common in women than in men.[2] Treatment of these disorders frequently includes surgical thyroidectomy, radioiodine therapy, or both, resulting in hypothyroidism that requires lifelong treatment with levothyroxine.

What advice should hypothyroid women be given about levothyroxine therapy when they become pregnant? One study clearly accepts that the dose of levothyroxine should be increased.[3] This study is at odds with several others that state either that no change in treatment is required, or that some women require an increase in thyroxine but that this is an uncommon occurrence.[4–7] The current study evaluates 20 women who required levothyroxine as a result of having had thyroid surgery, radioiodine therapy, or both. They were followed throughout pregnancy by means of biochemical testing of thyroid function.

## Methods

### *Patients Studied*

The patient population included 20 women, ranging in age from 16 to 38 years at the time of their first pregnancy. Eight of the patients had had surgery for thyroid cancer, most commonly total or near total thyroidectomy. Six other patients had undergone surgery for thyroid cancer followed by radioiodine 131 ablation. Five patients had undergone radioiodine therapy for Graves' disease. One had undergone a near-total thyroidectomy for a benign nodule that had enlarged in spite of thyroid suppressive therapy. She was studied twice, initially while on levothyroxine for suppression of the nodule and again while on levothyroxine after near-total thyroidectomy. The patients were studied before conception and were followed prospectively during the pregnancy, with measurements of thyrotropin (thyroid-stimulating hormone

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[TSH]) and free thyroxine ($FT_4$). The number of thyroid evaluations per patient varied from a minimum of two to a maximum of eight measurements. Some patients had a greater number of measurements throughout pregnancy because of abnormal results, indicating a need for adjustments in levothyroxine dosage, eg, a higher-than-normal TSH value necessitated an increase in levothyroxine. Patients were questioned about the amount of weight gain during the pregnancy.

### *Thyroid Function Tests*

$FT_4$ was measured using a two-step immunoradiometric assay (Clinical Assays, Incstar Corp, Stillwater, Minn), with a normal range of 0.8 to 2 ng/dL (10 to 26 pmol/L), an interassay coefficient of variation of 4.9%, and an intra-assay coefficient of variation of 3.4%. TSH was measured using a third-generation chemiluminescent assay (Corning Nichols Institute, San Juan Capistrano, Calif), with a normal range 0.4 to 4.5 μU/mL (0.4 to 4.5 mU/L), and an interassay coefficient of variation of 8.6% for samples of mean value 1.4 μU/mL (1.4 mU/L) and 6.0% for samples of mean value 7.86 μU/mL (7.86 mU/L).

### *Statistics*

TSH measurements before pregnancy were compared with peak values during pregnancy for each patient. One patient did not have a baseline measurement made in close proximity to the onset of pregnancy. Therefore, for statistical analysis using Student's paired *t* test, 19 paired TSH values were evaluated. Similarly, for $FT_4$ measurements, Student's paired *t* test was used to compare a total of 15 paired results: those obtained before pregnancy, and those representing the lowest value during pregnancy. The dosage of levothyroxine the patient was taking before pregnancy and the peak value required during pregnancy to normalize abnormal thyroid function test results also were compared for all 20 patients using Student's paired *t* test. One patient was followed while she was taking levothyroxine for a benign thyroid nodule during one pregnancy and while taking levothyroxine after thyroidectomy during her second pregnancy.

## Results

The mean TSH value before pregnancy was 0.88 μU/mL (0.88 mU/L) (standard error of the mean [SEM], 0.3). The mean peak TSH value during the pregnancy was 16.8 μU/mL (16.8 mU/L), SEM, 3.86; $P<.001$. In every patient, the baseline TSH value rose, and in every case, the TSH value rose above the upper limit of normal. The $FT_4$ level before conception was 1.63 ng/dL (21 pmol/L), SEM, 0.06, and during pregnancy 1.09 ng/dL (14 pmol/L), SEM, 0.08; $P<.001$. Only one $FT_4$ measurement fell below the defined normal range, and one other measurement was at the lower limit of normal, 0.8 ng/dL (10 pmol/L). The average change in levothyroxine dosage was an increase from 125 μg, SEM, 5, before pregnancy to 161 μg, SEM, 8.2, in the 20 patients during pregnancy. This difference is statistically highly significant ($P<.001$). The average increase in thyroid requirement (36 μg) and the average weight gain (35 lb±8) appear similar; however, the correlation coefficient was not statistically significant. After delivery, the requirement for levothyroxine returned to prepregnancy levels.

In the patient studied through two pregnancies, TSH measurements were low and remained low while she was taking 125 μg levothyroxine daily during the first pregnancy (pre-thyroidectomy). During the second pregnancy when she was athyrotic, her requirement for levothyroxine increased from 125 μg to 163 μg. After delivery, the requirement returned to 125 μg.

## Discussion

The data demonstrate that patients who do not have a thyroid reserve and are taking levothyroxine require an increase in the dosage of levothyroxine during pregnancy. Only one publication has described this finding,[3] and an analysis of reviews and textbooks[4–8] shows that these sources either make no comment on this issue or state that the prepregnancy replacement dosage is adequate during pregnancy. For example, Longcope[4] states that "there is no evidence that the dose of hormone needs to be changed during pregnancy provided that adequate replacement was given before conception." Becks and Burrow[5] agree that some women "require an increase in $T_4$ dose in pregnancy although this is uncommon." Laurberg[6] accepts that adjustment "is required in approximately one fourth of women during pregnancy, most often the dose must be increased." Camargo[7] reports that "there is no need to increase the dose of L-thyroxine during pregnancy." Mandel and colleagues[3] found that the dose had to be increased by 45%, which is more closely aligned with the required 29% increase described in this study.

What factors account for this apparent disagreement in the medical literature? It is important to recognize that the patients in our study had little or no functioning thyroid. Therefore, they were totally dependent on exogenous levothyroxine. It is conceivable that patients who are on levothyroxine for reasons such as suppression of

nodules have sufficient reserve for normal thyroid function if maintained on a stable dose of thyroxine during pregnancy. This is an issue that needs to be addressed. All 20 patients described in this report required more levothyroxine during pregnancy after the thyroid was removed or ablated with radioiodine 131.

The increase in thyroid-binding globulin in pregnancy causes a rise in total thyroxine and triiodothyronine.[9] This is associated with a decrease in $FT_4$, although the values usually do not drop below normal.[10] In the euthyroid patient who has a normally responsive thyroid, the TSH does not rise outside the normal range. When there is normal thyroid reserve, the gland can probably respond by increasing the secretion of thyroid hormones to maintain normal levels of $FT_4$ and TSH. If a fixed dosage of levothyroxine is entering the system, however, the change in binding proteins may shift $FT_4$ downward slightly and subsequently increase the TSH, as demonstrated in this study.

The dosage of levothyroxine given to most patients generally is closely related to weight. Although not precise for every patient, a dosage of slightly less than a microgram of levothyroxine per pound of body weight is a good general guideline. In this study, there was an increased requirement of 36 μg thyroxine, which correlated closely with the mean increase in weight of 35 lb. There was considerable variation among patients, however, and the correlation coefficient of increased thyroxine dosage did not meet statistical significance when compared with weight gain. Nevertheless, in several patients, the correlation was virtually identical. Although it is recognized that there is an increased basal metabolic rate in pregnancy, it has generally been accepted that the increase in basal metabolic rate is closely related to the weight gain caused by the embryo and placenta.[11]

There are data showing that iron can interfere with the absorption of thyroxine.[12] The effect is not large, but it is statistically significant. Based on these data, the women in the current study were advised to take thyroxine in the morning and prenatal vitamins, which contain iron, in the evening to minimize this interaction. The role of noncompliance was probably not a factor since these women, as are the vast majority of pregnant women, were most concerned about their own health and that of their unborn child.

## Conclusions

Women who have no thyroid reserve because of thyroid surgery or radioiodine, or both, require more thyroxine during pregnancy. The clinical implication is that patients should be evaluated at least once each trimester with measurement of $FT_4$ and TSH levels. If the TSH level rises above normal, the dosage of levothyroxine should be titrated upward. It is reasonable to consider either the next available strength of pill or a 25-μg increment, followed by TSH measurement after 6 weeks. The recommendation for reevaluating during each trimester is based on this study's findings that TSH levels changed throughout the course of pregnancy. It might be asked, "Why not empirically increase the dose of thyroid?" Among our patients, the change in requirement varied from 13 μg to 125 μg. Thus, it would appear more appropriate to base the adjustment on individual laboratory measurements. The dosage of levothyroxine should be decreased after delivery to the prepregnancy level and evaluated again with TSH measurement.

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