EDITORS' CHOICE —
THYROID HORMONE REPLACEMENT IN PREGNANCY

Adding two additional tablets of levothyroxine per week, when instituted immediately upon confirmation of pregnancy to women with known hypothyroidism significantly reduces the risk of maternal hypothyroidism throughout pregnancy

SUMMARY

BACKGROUND

Maternal hypothyroidism during the first half of pregnancy may result in serious harm to fetal development. As a consequence, it is important for pregnant women with hypothyroidism to maintain biochemical euthyroidism during gestation. Pregnant women thus must increase their levothyroxine dose during pregnancy, as the thyroid hormone requirement increases 20 to 40% during gestation. Yet how this should be accomplished remains uncertain.

METHODS

A total of 60 women with treated hypothyroidism who were newly pregnant or were planning to become pregnant were prospectively enrolled in this study. Once pregnant, the women were randomly assigned to increase their levothyroxine (L-T$_4$) by either two tablets per week (group A) or three tablets per week (group B). Biweekly thyroid-function tests were performed through midpregnancy and at 30 weeks of gestation, and levothyroxine doses were adjusted to maintain the target thyrotropin (TSH) concentrations. The primary objective of the study was to assess the efficacy of preventing maternal hypothyroidism and the safety of levothyroxine intervention.

Prior to pregnancy, data were collected to document the demographic characteristics of the women and the type of thyroid dysfunction and to confirm a stable dose of L-T$_4$ for at least 6 weeks. Newly pregnant women were enrolled only if they were less than 11 weeks pregnant and had normal baseline serum TSH concentrations for 6 months preceding enrollment in the study. Women with thyroid cancer were enrolled if thyroid-function tests confirmed a serum TSH of 0.01 to 2.5 mIU/L. Subjects without thyroid cancer were enrolled if prepregnancy thyroid-function tests confirmed a TSH of 0.05 to 5.0 mIU/L. Once pregnancy was suspected, patients had confirmatory serum human chorionic gonadotropin tests and the serum TSH, total thyroxine (T$_4$), and thyroid hormone binding ratio were measured.
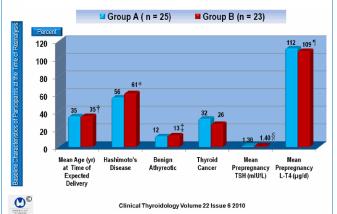
Subjects were then randomly assigned to increase their prepregnancy doses of L-T$_4$ by either two tablets per week (29%) (a total of nine tablets per week in group A) or three additional tablets per week (43%) (a total of 10 tablets per week in group B). Patients were instructed to take double doses of their current L-T$_4$ tablets on Saturdays and Wednesday (group A) or on Mondays, Wednesdays, and Fridays (group B). The patients were instructed to take L-T$_4$ on an empty stomach and to avoid calcium, iron, or prenatal vitamins within 4 hours

of L-T$_4$ ingestion. This was based on a 20 to 40% increased requirement of levothyroxine among pregnant women, which had been previously documented.

Patients returned for follow-up testing every 2 weeks until 20 weeks of gestation (midpregnancy) and once more at 30 weeks, during which approximately 10 serum samples of serum TSH, total T$_4$, and thyroid hormone binding ratio had been obtained in each patient; and L-T$_4$ dosage was adjusted every 4 weeks, at weeks 4, 8, 12, 16, 20 and 30 weeks according to the protocol. During the intervening weeks (6, 10, 14, and 18) the L-T$_4$ dosage was modified if TSH was 10 mIU/L or <0.01 mIU/L both in patients with hypothyroidism and those with thyroid cancer.

The estimated date of delivery was based on the first day of the woman's most recent menstruation or on a sonographic examination performed at the request of the treating obstetrician. The primary and secondary analysis was performed only on the 48 patients who completed the randomized protocol. A total of 10 women had a miscarriage shortly after enrollment in the study, 6 of whom had initial blood work that confirmed pregnancy but had not yet been assigned to a treatment group, and thus

Figure 1. This figure depicts the baseline data from 48 women with treated hypothyroidism who completed the study protocol. *P = 0.85 comparing mean age at the time of expected delivery in groups A and B. †P = 0.91 comparing mean pregnancy TSH in group A and group B. §P = 0.89 comparing prepregnancy L-T$_4$ in group A with that in group B. ‡P = 0.89 comparing mean prepregnancy requirement of L-T$_4$ (µg/dl) in group A versus group B. The data for this figure are derived from Table 2 of Yassa et al.

did not participate in the study, and 4 who were randomly assigned to the study protocol had no blood tests before the miscarriage occurred.

RESULTS

Patient demographics (Figure 1)

A total of 60 women with treated hypothyroidism were enrolled in the study, 48 of whom (80%) successfully completed the protocol (25 in group A and 23 in group B). The mean age of patients completing the protocol was 34.4 years. Miscarriage occurred in 10 women (16.6%), at a mean age 35.9 years and an average of 7 weeks of gestation, which was not different from the expected miscarriage rate among women of the same age in the study group. The miscarriages were one stillbirth at 20 weeks of gestation due to an incompetent cervix and one from a molar pregnancy (Figure 1).

The mean prepregnancy serum TSH concentration of the 12 women who did not complete the protocol was 1.2 µIU/ml, which was not significantly different from that in women who did complete the protocol (P = 0.81). Eight of these women were treated with L-T$_4$ for Hashimoto's disease, two had thyroid cancer, and two were athyreotic from benign disease (Figure 1). In this group, the mean prepregnancy L-T$_4$ requirement was 99 µg/day (P = 0.35), as compared with the 48 women who completed the protocol.

Among the 48 women who completed the protocol, 25 (52%) were randomly assigned to increase their L-T$_4$ to two extra tablets per week (group A). A total of 8 (32%) had a history of thyroid cancer, and 17 (68%) had hypothyroidism caused by Hashimoto's disease or ^{131}I ablation. A total of 23 women were randomly assigned to increase their L-T$_4$ dose by three extra tablets per week (group B); 6 of them had thyroid cancer (26%) and 17 (74%) had hypothyroidism due to Hashimoto's disease, surgery, or ^{131}I ablation for thyroid cancer. In all, 28 of 48 patients (58%) had hyperthyroidism due to Hashimoto's thyroiditis and 14 (29%) had thyroid cancer. The demographic data for these women as well as their mean prepregnancy TSH concentrations and L-T$_4$ requirements are shown in Figure 1.

The pregestational TSH was <2.5 mIU/L in 41 of 48 women (85%) and <3.0 mIU/L in 43 of 48 women (90%). For women with Hashimoto's disease, the mean serum TSH concentration was 1.8 mIU/L (range, 0.5 to 4.3), for women with benign athyreotic hypothyroidism, 1.5 mIU/L (range, 0.4 to 4.8), and for women with thyroid cancer it was 0.5 mIU/L (range, 0.1 to 0.9). Pregnancy was confirmed in all women 11 weeks before pregnancy. Enrollment occurred at a median of 5.5 weeks of pregnancy (mean, 6.3 weeks); nonetheless, on their initial postconception test, 13 of 48 women (27%) had serum TSH concentrations >5.0 mIU/L, which confirmed that L-T$_4$ replacement was inadequate in early gestation. Preconception TSH values in the 13 women revealed that 4 (31%) had values of <1.0 mIU/L, 8 (62%) had values of 1.0 to 2.5 µIU/ml, and 1 of 13 (8%) had values of 2.6 to 5.0 µIU/ml.
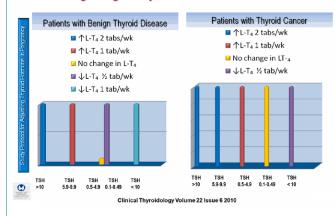
Protocol for Thyroid Hormone early Adjustment (Figure 2)

Increasing the L-T$_4$ dose at the time of entry into the study by either two or three additional tablets per week normalized the serum TSH at <5.0 mIU/L in all women for the remainder of the first trimester. Two women in group A (8%), both of whom had athyreosis, one after thyroidectomy and the other for benign disease, had an elevated serum TSH of 5.1 and 6.2 µIU/ml during pregnancy at weeks 14 and 16, respectively, requiring a further increase in L-T$_4$. In group B, 1 of 23 women (4%) had a serum TSH of 7.7 and 7.4 µIU/ml during pregnancy at weeks 14 and 16, respectively, which required a similar increase in L-T$_4$. This woman had Hashimoto's disease. No other serum TSH concentrations >5.0 mIU/L occurred during the study.

For all women who completed the study protocol, the mean TSH concentration decreased throughout the first trimester, especially during weeks 10 to 14 of gestation, and thereafter a normal serum TSH was maintained. The initial L-T$_4$ augmentation early in pregnancy caused suppression of TSH to <0.5 µIU/ml (<0.1 µIU/ml with thyroid cancer) in 8 of 25 (32%) women in group A, as compared with 15 of 23 (65%) women in group B (P<0.01). A total of 78% of these events occurred before gestational week 14, although the mean serum TSH concentration was only mildly below the lower reference range as defined in nonpregnant women. In patients without thyroid cancer, a mean TSH of 0.3 mIU/L (range, 0.06 to 0.44 mIU/L) triggered an L-T$_4$ dose reduction. Whereas in women with thyroid cancer, the TSH trigger averaged 0.06 µIU/ml (range, 0.01 to 0.09). Seventeen of these 23 women (74%) had a free T$_4$ index (FTI) within the accepted reference range of 10.8 to 13.1 (mean, 11.7).

However, during this study, new data were released providing trimester-specific TSH reference ranges in 13,000 pregnant women without thyroid dysfunction, indicating that the 2.5th percentile, and thus the lower limit, in a healthy pregnant women during the first trimester was 0.1 IUm/L, and the 97.5th percentile (the upper reference limit) was 2.5, 3.0, and 3.0 mIU/L in the first, second, and third trimesters, respectively. Using these new reference data, group A had only 2 patients (8%) with a TSH <0.01 µIU/ml at any point during pregnancy. Thus, a woman with benign athyreotic hypothyroidism experienced a TSH of 0.05 µIU/ml and an FTI of 8.4 at pregnancy week 14, and a patient with thyroid cancer experienced a TSH of 0.05

Figure 2. This figure shows the protocol for early adjustment for L-T$_4$ early in pregnancy for patients with benign thyroid disease or thyroid cancer. The data for this figure were derived from Table 1 of Yassa et al.

µIU/ml and an FTI of 11.93 at pregnancy week 16. In group B, 6 of 23 patients (26%) had a serum TSH <0.01 µIU/ml during pregnancy. Thus, five patients with thyroid cancer experienced TSH and FTI values of 0.09 mIU/L and 10.5 at gestation week 10; 0.09 µIU/ml and 10.1 at week 14; 0.01 µIU/ml and 13.1 at week 8; 0.05 µIU/ml and 9.8 at week 12; and 0.02 µIU/ml and 12.2 at week 10. One patient in group B who had Hashimoto's disease experienced a TSH of 0.06 µIU/ml with an FTI of 10.8 at week 16. Thus, among all 48 patients, FTIs were elevated beyond the reference limits in only 4 of 8 patients at the time TSH was <0.01 µIU/ml.

The data were analyzed separately to determine the proportion of patients with serum TSH concentrations from 2.5 to 5.0 µIU/ml at any point during the investigation. Although two subjects in group A experienced a single TSH concentration >5.0 µIU/ml at least once during the study, eight women experienced TSH concentrations of 2.5 and 5.0 µIU/ml during the study. Among seven of eight women, this was a single isolated occurrence throughout all of gestation, while one woman had two separate values in this range. In group B, four patients experienced a single TSH concentration between 2.5 and 5.0 mIU/L during the study. None of the subjects experienced an FTI of <5.0 at any point throughout the study.

Multivariate Analysis of L-T$_4$ Dose as It Relates to Subsequent Serum TSH Suppression (Figure 3)

To identify which variable predicted an increased risk for TSH suppression after L-T$_4$ treatment intervention, data from all 48 patients who completed the protocol were analyzed. In all, 18 of 29 women (37.5%) with prepregnancy serum TSH concentrations <01.5 µIU/ml required L-T$_4$ dose reductions during pregnancy as compared with 5 of 19 women (33%) with prepregnancy serum TSH concentrations of 1.5 µIU/ml or higher; the odds ratio (OR) was 4.6 (95% confidence interval [CI], 1.3 to 16.2). Likewise, 20 of 32 women (62.5%) receiving prepregnancy L-T$_4$ doses of at least 100 µg/day required L-T$_4$ reductions during pregnancy, as compared with 3 of 16 women (19%) receiving less than 100 µg/dl (OR, 7.2; 95% CI, 1.7 to 30.6). Lastly, 13 of 20 (65%) women with athyreotic hypothyroidism due to surgery or ^{131}I ablation, required L-T$_4$ dose reductions during pregnancy, as compared with 10 of 28 women (36%) with Hashimoto's disease (OR, 3.3; 95% CI, 1.1 to 11.1) (Figure 3).
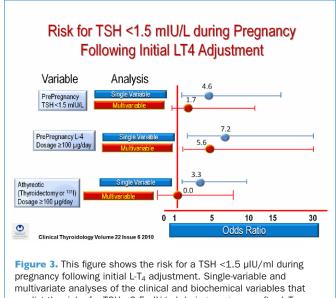
Multivariate analysis demonstrated that a prepregnancy L-T$_4$ dose of at least 100 µg/day was independently predictive of the risk for subsequent TSH suppression (OR, 5.6; 95% CI, 1.3 to 29.3; P = 0.02). Prepregnancy TSH concentration <1.5 µIU/ml

(OR, 1.7; 95% CI, 0.6 to 12.6; P =0.19) and having athyreosis (OR, 0.0; 95% CI, 0.2 to 5.0; P = 0.90) were not statistically significant (Figure 3).

Lastly, to investigate the optimal frequency of TSH evaluation after an initial L-T$_4$ dose increase, the 25 patients in group A who completed the protocol after an increase in L-T$_4$ dosage of two tablets per week were analyzed. Reviewing all TSH concentrations in these 25 patients documented 26 abnormal TSH values that were outside the range of 0.01 to 2.5 µIU/ml and that triggered a dose adjustment as per the protocol. After analyzing the effectiveness of an every-4-week testing protocol, 24 of 26 (92%) abnormal TSH concentrations would have been detected regardless of an increased interval between TSH tests, and if an every-6-week protocol had been followed, abnormal TSH values would have been detected.

CONCLUSION

An increase of two levothyroxine tablets at the time pregnancy is confirmed significantly reduces the risk for maternal hypothyroidism during the first trimester and mimics normal physiology. The authors recommend monitoring serum TSH levels every 4 weeks through midgestation.

Figure 3. This figure shows the risk for a TSH <1.5 µIU/ml during pregnancy following initial L-T$_4$ adjustment. Single-variable and multivariate analyses of the clinical and biochemical variables that predict the risk of a TSH <0.5 µIU/ml during pregnancy after L-T$_4$ adjustment are also shown. This figure is adapted from Figure 2 by Yassa et al.

COMMENTARY

When thyroid deficiency occurs simultaneously in a pregnant woman and her fetus, the child's neuropsychological development is adversely affected (1,2). Moreover, hypothyroidism is common among women of childbearing age, and this poses a major threat to the fetus. This is compounded by an increased demand on T_4 requirements that occurs very early—within 4 to 5 weeks—of pregnancy (3), and the demand increases through midgestation at 16 to 20 weeks and is then sustained until delivery. To protect the fetus, L-T_4 must be administered in a way that replicates this pattern of L-T_4.

Yassa et al. found that merely adding two tablets of L-T_4 per week, when instituted immediately upon confirmation of pregnancy, significantly reduced the risk of maternal hypothyroidism throughout pregnancy. This protocol prevents maternal TSH elevation to >2.5 mIU/L and >5.0 mIU/L in 85% and 100% of women, respectively, thus reducing the risk of maternal hypothyroidism throughout pregnancy.

This protocol was found superior to adding three tablets of L-T_4 per week. Patients who have athyreosis require a prepregnancy L-T_4 dose of at least 100 µg/dl and those with prepregnancy serum TSH concentrations below 1.5 IUm/L are at highest risk for subsequent L-T_4 modification after the initial L-T_4 intervention.

The authors point out that this important recommendation can be conveyed to patients during prenatal counseling by their endocrinologist, obstetrician, or primary care physician, thus reducing the risk for maternal hypothyroidism and its harmful impact. It should be noted that monitoring thyroid function approximately once monthly is required through midpregnancy because a minority of patients may require L-T_4 modifications to maintain appropriate TSH levels. The authors provide the caveat that this is largely predicted by assessment of a woman's prepregnancy L-T_4 requirement, TSH concentrations, and underlying cause of thyroid dysfunction.

This important study should be read by physicians and other health care providers who provide information to women with hypothyroidism who may become pregnant. The authors' discussion in this article contains considerable insight into this important problem.

— **Ernest L. Mazzaferri, MD MACP**

References

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