EDITORS' CHOICE —
TSH LEVELS IN PREGNANCY

TSH levels between 2.5 and 5.0 in first-trimester thyroid antibody-negative women are associated with a significant increase in the rate of spontaneous miscarriage

Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab. June 9, 2010. doi:10.1210/jc.2010-0340

SUMMARY

BACKGROUND

The definition of what comprises a normal thyrotropin (TSH) during pregnancy has been changing. Although thyrotropin (TSH) values of 4.0 to 5.0 mIU/L were considered normal in the past, more recent opinions suggest that first-trimester TSH values >2.5 mIU/L, and second- and third-trimester values >3.0 µIU/ml are outside the normal range. This is reflected in the Endocrine Society's 2007 guidelines on thyroid and pregnancy, which recommend that TSH values in pregnant women on levothyroxine therapy should be <2.5 mIU/L in the first trimester and <3.0 mIU/L after the first trimester. The TSH in the first trimester is largely driven by human chorionic gonadotropin, which cross-reacts at the TSH receptor, thus creating a decline in first-trimester TSH levels. The objective in this study was to assess the pregnancy loss and preterm delivery rate in first-trimester thyroid peroxidase antibody–negative women with TSH values between 2.5 and 5.0 mIU/L.

Current normative data support a revised normal range for TSH in pregnancy, although the precise upper limit of normal varies somewhat among studies. The authors began with the notion that in order to accurately identify the normal range for TSH during pregnancy, it is of vital importance to define the clinical implications, starting with pregnancy loss and preterm delivery, of an untreated first-trimester TSH in a range that had previously been considered normal.

SUBJECTS AND METHODS

The current study is a component of a prospective study of 4657 women who were screened for TSH and thyroid peroxidase antibody within the first 11 weeks of gestation in southern Italy. To be eligible for the study, women had to have no history of a thyroid disorder and a spontaneous singleton pregnancy. The women were randomly assigned to a universal screening group or a case-finding group and stratified as high risk or low risk for thyroid disease. Both the high- and low-risk women in the universal screening group and the high-risk women in the case-finding group had their serum TSH and thyroid peroxidase antibody levels tested immediately. During pregnancy, the women who were antibody-positive with a TSH >2.5 µIU/ml were treated with levothyroxine and the women with a suppressed TSH and an elevated free thyroxine (FT_4) were classified as hyperthyroid and were referred to an endocrinologist. Maternal and neonatal outcomes were assessed.

All of the women in the study who were thyroid antibody–negative, not classified as hyperthyroid, and had a serum TSH of ≤5.0 mIU/L were evaluated, but none of these women were treated during pregnancy. Women were stratified into two groups: group A had a serum TSH <2.5 mIU/L and was classified as euthyroid; group B had a serum TSH between 2.5 and 5.0 µIU/ml and was classified as having subclinical hypothyroidism. The study outcome was based on the percentage of pregnancy loss, which included miscarriage before 20 weeks, stillbirth after 20 weeks, preterm delivery at 34 to 37 weeks, and very preterm delivery at <34 weeks, in each group.

RESULTS

Stratification of Serum TSH and FT_4 Levels in Group A and Group B (Figure 1)

A total of 4123 women were thyroid antibody–negative, with a TSH of 5.0 mIU/L or lower, and were not hyperthyroid. Group A comprised 3481 women (84.4%), and group B comprised 642 women (15.6%). According to the study design, the median TSH in group A was significantly lower than the TSH in group B (0.82 vs. 3.14 mIU/L; P<0.001). Mean FT_4 levels were significantly higher in group A as compared with group B (12.2 vs. 10.6 pmol/L, P<0.01) *(Figure 1)*. The rate of spontaneous pregnancy loss was 127 of 3481 women in group A (3.6%), which was significantly lower than that in group B, which was 39 of 642 women (6.1%; P<0.006).

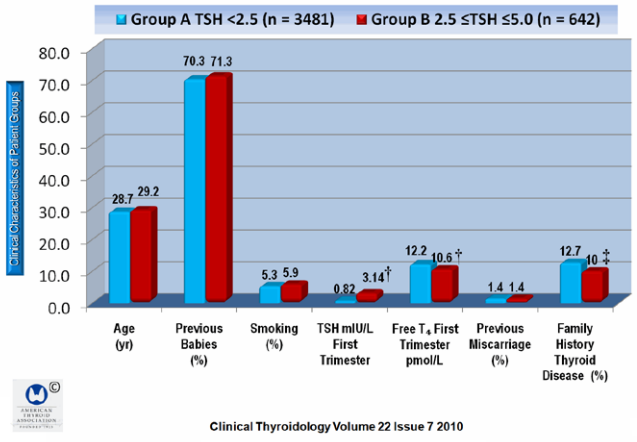

Figure 1. This figure shows the demographic information, pregnancy history, clinical information, and results of thyroid-function tests for women broken down by group. Group A TSH levels are below 2.5 mIU/L and group B TSH levels are between 2.5 and 5.0 mIU/L. †P<0.01. ‡P<0.05. Women in group A were more likely to have a family history of thyroid disease. There was no difference in mean gestational week of the initial visit between groups.

Rate of Spontaneous Pregnancy Loss (Figure 2)

The rate of spontaneous pregnancy loss in Group A (3.6%, n – 127 of 3481 was significantly lower than the rate of spontaneous pregnancy loss in group B (6.1%, n = 39 of 652 (P = 0.006). *(Figure 2)*. There was no difference between groups in the rates of preterm delivery in group A (1.85%, vs. 0.93% in group B; P = not significant).

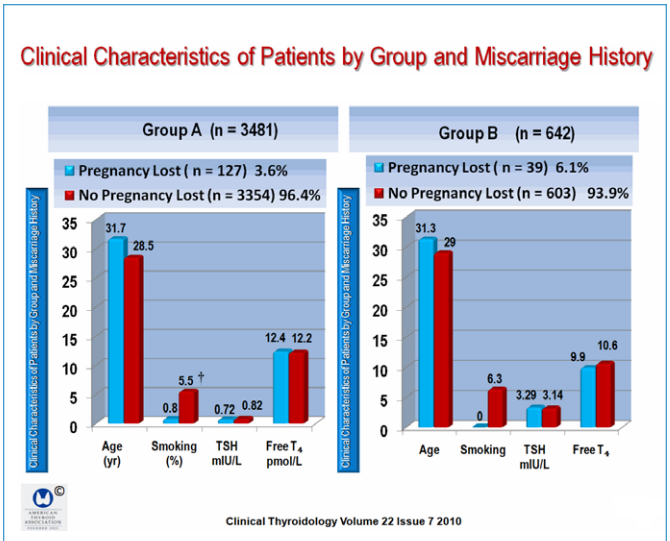

Figure 2. This figure presents age, obstetrical history, clinical data from thyroid-function tests, and mean gestational age of pregnancy loss in groups A and B broken down by the presence or absence of pregnancy loss. There was a slight but statistically significant increase in smoking rates in women who did not have a miscarriage (P<0.05).

The FT_4 was significantly higher in group A as compared with group B; however, the rate of spontaneous pregnancy loss, preterm delivery, or very preterm delivery was not related to FT_4 levels *(Figure 2)*. There were no differences in maternal age, pregnancy history, or thyroid function tests in women who had a miscarriage in each group versus those who did not miscarry. There was a slight but statistically significant increase in smoking rates in women who did not miscarry in group A. The mean gestational age at the time of the first obstetrical visit and mean gestational age at the time of pregnancy loss were essentially identical in all groups.

To further assess the impact of TSH levels, a simple logistic-regression analysis was performed to predict miscarriage from TSH level and smoking status. The odds ratio (OR) for each point of TSH was 1.157; 95% confidence interval [CI], 1.002 to 1.336; P = 0.047), suggesting a continuous relationship between TSH and miscarriage, controlling for smoking. The odds were lower for smokers than nonsmokers (OR, 0.120; 95% CI, 0.014, 0.732, controlling for the TSH level).

CONCLUSION

TSH levels between 2.5 and 5.0 in first-trimester thyroid antibody–negative women is associated with a significant increase in the rate of spontaneous pregnancy loss as compared with the first-trimester thyroid antibody–negative women with TSH levels <2.5 µIU/ml, excluding women with hyperthyroidism.

COMMENTARY

This study shows for the first time that serum TSH levels between 2.5 and 5.0 in thyroid antibody–negative women in the first trimester is associated with a significant increase in the rate of spontaneous fetal loss as compared with first-trimester thyroid antibody-negative women with TSH levels <2.5 mIU/L, except for women with hyperthyroidism. However, there were no differences in the rates of preterm delivery or very preterm delivery. The authors conclude that the increased rates of spontaneous fetal loss in women with TSH levels between 2.5 and 5.0 mIU/L provides strong support to redefine the normal TSH during pregnancy, especially in the first trimester.

Negro et al. summarized the changing opinions concerning the normal range for TSH levels during pregnancy, especially during the first trimester, which has been investigated in a number of studies. For example, over the past decade, the normal TSH range has been studied by Panesar et al. (1), who performed a prospective study of 343 Chinese women and found that the normative range for first-trimester TSH levels were 0.03 to 2.3 mIU/L. Pearce et al. (2) found in a study of 585 antibody-negative women in Boston that before 14 weeks of gestation, TSH levels ranged between 0.04 and 3.6 mIU/L. Another study, by Stricker et al. (3) found that the interpretation of thyroid-function tests in pregnant women using nonpregnancy reference intervals could potentially result in misclassification of a significant percentage of the results, including TSH and thyroid peroxidase autoantibody (anti-TPOAb). Negro et al. found that the overall consistency in the TSH ranges reported for the first-trimester antibody-negative women reached a consensus centering on the lower limit of TSH of 0.04 and an upper range of normal of 2.5 mIU/L.

A recent study from the Netherlands by Benhadi et al. (4) found in a cohort of pregnant women without overt thyroid dysfunction that the risk of child loss increased with higher levels of maternal TSH and that maternal FT_4 concentrations and child loss were not associated. The authors concluded that pregnancy outcome might be improved by treating women with mildly elevated TSH, or even with normal TSH if TPOAb is present.

Negro et al. concluded that recent normative studies confirm that a redefinition of the TSH is required, resulting in a shift to a range of approximately 0.03 to 2.5 mIU/L, and that a TSH >2.5 mIU/L not only exceeds the 97.5th percentile for the first trimester of pregnancy but also is associated with serious physiologic consequences. Negro et al. (5) recently reported in a prospective, randomized trial that that treating thyroid TPOAb-positive women with TSH levels ≥2.5 mIU/L results in a significant decrease in maternal and neonatal complications.

The authors propose that a similar study is now needed for thyroid antibody-negative women with a TSH >2.5 mIU/L, which seems warranted, based on the current findings.

— Ernest L. Mazzaferri, MD, MACP

References

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