

## Increased Pregnancy Loss Rate in Thyroid Antibody Negative Women with TSH Levels between 2.5 and 5.0 in the First Trimester of Pregnancy

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**Context:** The definition of what constitutes a normal TSH during pregnancy is in flux. Recent studies suggested that the first trimester upper limit of normal for TSH should be 2.5 mIU/liter.

**Objective:** The objective of the study was to evaluate 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/liter.

**Design:** The present study is a component of a recently published large-scale prospective trial that evaluated the impact of levothyroxine treatment on maternal and neonatal complications in thyroid peroxidase-positive women with TSH levels above 2.5 mIU/liter. The present study evaluated 4123 thyroid peroxidase antibody-negative women with TSH levels at or below 5.0 mIU/liter. Women were divided into two groups based on their initial TSH: group A, TSH level below 2.5 mIU/liter, excluding hyperthyroid women defined as an undetectable TSH with an elevated free T<sub>4</sub>, and group B, TSH level between 2.5 and 5.0 mIU/liter.

**Setting:** The study was conducted at two ambulatory clinics of community hospitals in southern Italy.

**Patients:** A total of 4123 women were evaluated.

**Intervention:** There was no intervention.

**Main Outcome Measures:** The incidence of pregnancy loss and preterm delivery in group A as compared with group B was measured.

**Results:** The rate of pregnancy loss was significantly higher in group B as compared with group A (6.1 vs. 3.6% respectively,  $P = 0.006$ ). There was no difference in the rate of preterm delivery between the two groups.

**Conclusions:** The increased incidence of pregnancy loss in pregnant women with TSH levels between 2.5 and 5.0 mIU/liter provides strong physiological evidence to support redefining the TSH upper limit of normal in the first trimester to 2.5 mIU/liter. (*J Clin Endocrinol Metab* 95: E44–E48, 2010)

The definition of what constitutes a normal TSH during pregnancy is changing. Whereas TSH values of 4.0–5.0 mIU/liter were once considered normal, a consensus is emerging that first-trimester values above 2.5 mIU/liter and second- and third-trimester values exceeding 3.0 mIU/liter, are outside the normal range. This change is reflected in The Endocrine Society's 2007 guidelines on thyroid and pregnancy, which recommended that TSH values in pregnant women on levothyroxine therapy should be less than 2.5 in the first trimester and less than 3.0 mIU/liter in the subsequent trimesters (1). The decrease in the upper range of TSH during pregnancy, and in particular in the first trimester, is driven by elevations of human chorionic gonadotropin, which cross-react at the TSH receptor and cause a concomitant decline in first-trimester TSH levels (2).

Solid normative data support a revised normal range for TSH in pregnancy, although the exact upper limit of normal varies mildly between studies. Of critical importance is 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. For purposes of the present study, based on The Endocrine Society Guidelines (1) and recently published normative data (3–6), we chose to evaluate the impact of TSH levels between 2.5 and 5.0 mIU/liter.

Prior research demonstrated an increased incidence of spontaneous pregnancy loss in women with maternal overt hypothyroidism (7). However, data on subclinical hypothyroidism (defined as a TSH  $\geq$  5.0 mIU/liter) and miscarriage have been conflicting with some, but not all, studies showing an increased rate of pregnancy loss (8, 9). Both overt and subclinical hypothyroidism has been associated with preterm delivery (10). Casey *et al.* (11) in a prospective study of 17,298 Texan women reported that women with TSH levels before 20 wk gestation that exceeded the percentile of 97.5 had a higher rate of preterm delivery than euthyroid controls (4.0 vs. 2.5%,  $P < 0.05$ ). Thyroid antibodies were not reported in the study by Casey *et al.* Stagnaro-Green *et al.* (12) found an increased rate of very preterm delivery (before 32 wk gestation), but not preterm delivery, in women with TSH levels above 3.0. Neither study had a maximum TSH level.

To our knowledge, the present study is the first to evaluate the relationship between spontaneous pregnancy loss, preterm delivery, and first-trimester TSH values between 2.5 and 5.0 mIU/liter. Thyroid antibody-positive euthyroid women in the first trimester have been demonstrated to have both increased miscarriage rates (13, 14) and increased rates of preterm delivery (15). Consequently, to remove this confounding factor, antibody-pos-

itive women have been excluded from the present investigation.

## Subjects and Methods

The present study is a component of a prospective study in 4657 women who were screened for TSH and thyroid peroxidase antibody within the first 11 wk of gestation in southern Italy (16). Eligibility criteria included no prior history of a thyroid disorder and a spontaneous singleton pregnancy. 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. All women in the universal screening group (both high risk and low risk) and high-risk women in the case finding group had TSH and thyroid peroxidase antibody performed immediately. Women in the case finding group had their sera tested postpartum. During pregnancy, antibody-positive women with a TSH above 2.5 mIU/liter were treated with levothyroxine. Women with a suppressed TSH and elevated free T<sub>4</sub> were classified as hyperthyroid and referred to the endocrinologist. Maternal and neonatal outcomes were assessed.

The present study evaluated all women in the study who were thyroid antibody negative, not classified as hyperthyroid, and had a TSH of 5.0 mIU/liter or below. None of these women were treated during pregnancy. Two groups of women were formed: group A had a TSH less than 2.5 mIU/liter and were classified as euthyroid; group B had a TSH between 2.5 and 5.0 mIU/liter and were classified as subclinical hypothyroidism. The outcome variable of the study was the percentage of pregnancy loss (includes miscarriage before 20 wk and stillbirth after 20 wk), preterm delivery (34–37 wk), and very preterm delivery (<34 wk) in each group. Statistical analysis was performed using Fisher's exact test.

## Results

Four thousand one hundred twenty-three women were thyroid antibody negative, had a TSH of 5.0 mIU/liter or below, and were not hyperthyroid. A total of 84.4% of the women were in group A ( $n = 3481$ ) and 15.6% of women were in group B ( $n = 642$ ). Table 1 presents age, prior obstetrical history, clinical data, and thyroid function tests of groups A and B. Per design of the study, the median TSH level in group A is significantly lower than group B (0.82 vs. 3.14 mIU/liter, Mann-Whitney  $U = 0$ ,  $P < 0.001$ ). Mean free T<sub>4</sub> levels were higher in group A vs. group B (12.2 vs. 10.6,  $P < 0.01$ ). Women in group A were slightly more likely to have a family history of thyroid disease. There was no difference in mean gestational week of the initial visit between groups.

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 642) ( $P = 0.006$ ). There were five stillbirths in group A (five of 127 = 3.9%) and two stillbirths in group B (two of 39 = 5.1%), There was no difference between groups

**TABLE 1.** Clinical characteristics of patients by group

	Group A TSH < 2.5 (n = 3481)	Group B 2.5 ≤ TSH ≤ 5.0 (n = 642)
Age (yr)	28.7 ± 5	29.2 ± 5
Previous babies (%)	2447 (70.3%)	458 (71.3%)
Smoking (%)	185 (5.3%)	38 (5.9%)
First gynecological visit (wk)	8.8 ± 1.6	8.9 ± 1.5
TSH first trimester (mIU/liter), median (interquartile range) <sup>a</sup>	0.82 (0.36–1.40)	3.14 (2.79–3.44)
Free T <sub>4</sub> first trimester (pmol/liter) <sup>a</sup>	12.2 ± 2.1	10.6 ± 2.2
Family history of thyroid disease (%) <sup>b</sup>	443 (12.7%)	64 (10%)
Goiter (%)	29 (0.8%)	4 (0.6%)
Symptoms of hypo-/hyperthyroidism (%)	267 (7.7%)	45 (7%)
Type 1 diabetes/autoimmune disease (%)	34 (1%)	6 (0.9%)
Irradiation (%)	1 (0.03%)	1 (0.1%)
Previous miscarriage/preterm deliveries (%)	50 (1.4%)	9 (1.4%)

Demographic information, pregnancy history, clinical information, and thyroid function tests for women are broken down by group. Group A TSH levels are below 2.5 mIU/liter; group B TSH levels are between 2.5 and 5.0 mIU/liter.

<sup>a</sup>  $P < 0.01$ .

<sup>b</sup>  $P < 0.05$ .

in the rates of preterm delivery (group A, 4.7% *vs.* group B, 5.1%,  $P = \text{ns}$ ) or very preterm delivery (group A, 1.85% *vs.* group B, 0.93%,  $P = \text{ns}$ ). Free T<sub>4</sub> was significantly higher in group A compared with group B. However, the rate of spontaneous pregnancy loss, preterm delivery, or very preterm delivery was not related to free T<sub>4</sub> levels. Table 2 presents age, prior obstetrical history, clinical data, thyroid function tests, and mean gestational age of pregnancy loss in groups A and B broken down by presence or absence of pregnancy loss. There were no differences in maternal age, pregnancy history, or thyroid function tests in women who miscarried in each group *vs.* 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. Mean gestational age at the time of the first obstetrical visit, and mean gestational age at the time of pregnancy loss, was virtually identical in all four groups.

To further explore the impact of TSH levels, we fit a simple logistic regression to predict miscarriage from TSH level (treated as an untransformed continuous variable) and smoking status. Among the women in our sample the odds ratio for each point of TSH was 1.157 (95% confidence interval 1.002, 1.336,  $P = 0.047$ ), suggesting a continuous relationship between TSH and miscarriage, controlling for smoking. As in the univariate analysis, the odds of miscarriage were lower for smokers than non-smokers (odds ratio 0.102, 95% confidence interval 0.014, 0.732,  $P = 0.023$ ), controlling for TSH level.

**TABLE 2.** Clinical characteristics of patients by group and miscarriage history

	Group A (n = 3481)		Group B (n = 642)	
	Pregnancy loss (n = 127) (3.6%)	No pregnancy loss (n = 3354) (96.4%)	Pregnancy loss (n = 39) (6.1%)	No pregnancy loss (n = 603) (93.9%)
Age (yr)	31.7 ± 3.1	28.5 ± 5.0	31.3 ± 2.4	29.0 ± 5.2
Previous babies (n)	88 (69.3%)	2359 (70.3%)	28 (71.8%)	430 (71.3%)
Smoking (%)	1 (0.8%)	184 (5.5%) <sup>a</sup>	0 (0.0%)	38 (6.3%)
First gynecological visit (wk)	8.9 ± 1.5	8.8 ± 1.6	8.8 ± 1.5	8.9 ± 1.5
Week of pregnancy loss	11.7 ± 3.7		11.8 ± 3.6	
TSH first trimester (mIU/liter), median (interquartile range)	0.72 (0.30–1.33)	0.82 (0.36–1.40)	3.29 (2.79–3.61)	3.14 (2.79–3.43)
Free T <sub>4</sub> first trimester (pmol/liter)	12.4 ± 2.2	12.2 ± 2.1	9.9 ± 2.4	10.6 ± 2.1
Family history of thyroid disease (%)	13 (10.2%)	430 (12.8%)	7 (17.9%)	57 (9.4%)
Goiter (%)	0 (0%)	29 (0.9%)	0 (0%)	4 (0.7%)
Symptoms of hypo-/hyperthyroidism (%)	7 (5.5%)	260 (7.7%)	3 (7.7%)	42 (7%)
Type 1 diabetes/autoimmune disease (%)	0 (0%)	34 (1%)	0 (0%)	6 (1%)
Irradiation (%)	0 (0%)	1 (0.03%)	0 (0%)	1 (0.2%)
Previous miscarriage/preterm deliveries (%)	3 (2.4%)	47 (1.4%)	0 (0%)	9 (1.5%)

Demographic information, pregnancy history, clinical information, thyroid function tests, and mean week of pregnancy loss are broken down by group and whether pregnancy loss occurred. Group A TSH levels are below 2.5 mIU/liter; group B TSH levels are between 2.5 and 5.0 mIU/liter.

<sup>a</sup>  $P < 0.05$  for comparison between miscarriage and no miscarriage subgroups within group.

## Discussion

The present study demonstrated, for the first time, that 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 when compared with first-trimester thyroid antibody-negative women with TSH levels less than 2.5 mIU/liter (excluding hyperthyroid women). No differences were seen in the rates of preterm delivery or very preterm delivery. The increased rate of pregnancy loss in women with TSH levels between 2.5 and 5.0 mIU/liter adds strong support to redefining the normal range of TSH during pregnancy, especially in the first trimester.

Over the last decade, the normative range for TSH levels during pregnancy has been an area of increasing investigation. Panesar *et al.* (3) reported in a prospective study of 343 Chinese women a normative range for first-trimester TSH levels of 0.03–2.3 mIU/liter. Pearce *et al.* (4) studied 585 thyroid antibody-negative women (in Boston, MA) before 14 wk gestation and found 95% of TSH levels fell between 0.04 and 3.6 mIU/liter. Gilbert *et al.* (5) studied 1817 thyroid antibody-negative Australian women between 9 and 13 wk gestation and reported a reference range of 0.02–2.15 mIU/liter. Stricker *et al.* (6) screened 783 thyroid antibody-negative women from the Geneva, Switzerland, area and reported the percentile range of 2.5–97 as 0.08–2.83 mIU/liter. Overall, there has been remarkable consistency in the TSH ranges reported for first-trimester antibody-negative women, with a consensus centering around a lower limit of normal of 0.04 and upper range of normal of 2.5.

Benhadi *et al.* (17) recently reported the relationship between TSH levels (after excluding overt hypothyroidism, classified as a TSH > 5.6 mIU/liter with a free T<sub>4</sub> < 7.7 pmol/liter), and child loss, defined as a combination of miscarriage or fetal or neonatal death in 2497 Dutch women. The mean gestational age at entry into the study was 13 wk and women enrolled after 27 wk were excluded from the analyses. The study found a 60% increase in child loss for every doubling of the TSH concentration. The majority of the child loss was through either fetal or neonatal death (16 of 27), compared with miscarriage (11 of 27), reflecting the late gestational age at initial screening. The authors conclude that “... pregnancy outcome might be improved by treating women with mildly elevated TSH (as in subclinical hypothyroidism) or even with normal TSH (if TPO-Ab are present).”

The strengths of the present study are the large size of the cohort, the exclusion of women who were thyroid peroxidase antibody positive, and its prospective nature. Limitations of the study include the fact that the popula-

tion consists of women from a single geographic area (southern Italy) which has a history of mild iodine deficiency. As demonstrated by a recent study by Moleti *et al.* (18), also performed in southern Italy, iodine deficiency plays a pivotal role in favoring thyroid impairment during gestation. Another potential shortcoming of the study is that thyroglobulin antibody was not measured, and therefore, it should be assumed that a small percentage of women would have been thyroglobulin antibody positive. Because thyroglobulin antibody-positive (thyroid peroxidase negative) women in the first trimester may develop thyroid impairment as pregnancy proceeds, this may have impacted the results of the study. Finally, it should be noted that there is a slight increase in smoking incidence in women in group A who did not have a pregnancy loss compared with women in group A who had a pregnancy loss. The reason for this is unclear.

In 2004, at the conclusion of a Centers for Disease Control and Prevention-sponsored conference on thyroid and pregnancy, multiple questions were generated for further research including “. . . what the TSH concentration should be to make a diagnosis of subclinical hypothyroidism . . .” (19). The data to answer that question now exist. Recent normative studies confirm that a redefinition is required, resulting in a shift to a range of approximately 0.03–2.5 mIU/liter. The present study demonstrates that TSH levels slightly above this range (2.5–5.0 mIU/liter) are linked to an increased rate of pregnancy loss. It can be concluded therefore that a TSH above 2.5 mIU/liter not only exceeds the percentile of 97.5 for the first trimester of pregnancy but also is associated with serious physiological consequences. Negro *et al.* (16), in a prospective randomized trial, recently reported that treating thyroid antibody-positive women with TSH levels of 2.5 mIU/liter or above results in a significant decrease in maternal and neonatal complications. A similar study is now needed for thyroid antibody-negative women with a TSH above 2.5 mIU/liter.

## Acknowledgments

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Disclosure Summary: R.N., A.S., R.G., A.T., T.M., and A.S.-G. have nothing to declare.

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