# Thyroid Antibody Positivity in the First Trimester of Pregnancy Is Associated with Negative Pregnancy Outcomes

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**Context:** Thyroid antibody positivity during pregnancy has been associated with adverse outcomes including spontaneous miscarriage, recurrent miscarriage, and preterm delivery.

**Objective:** The objective of the study was to determine whether thyroid antibody positivity in the first trimester of pregnancy in euthyroid women was associated with maternal and neonatal adverse outcomes.

**Design:** The present trial is a component of a prospective trial published in 2010 that evaluated screening for thyroid disease during pregnancy and the impact of levothyroxine therapy in women who were thyroid peroxidase positive with a TSH above 2.5 mIU/liter. The present study compared 14 maternal and neonatal adverse outcomes in 245 women who were euthyroid (TSH $<$ 2.5 mIU/liter) and thyroid peroxidase positive in the first trimester to 3348 women who were euthyroid and thyroid peroxidase negative in the first trimester.

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

**Patients:** The study consisted of 3593 women.

**Intervention:** There was no intervention.

**Main Outcome Measures:** The main outcome measures were 14 maternal and neonatal complications.

**Results:** The main result was an increase in very preterm delivery ($<$34 wk gestation at delivery) [4.5 *vs.* 1.8%; $\chi^2$(df = 1) = 8.58; $P$ = 0.003] and respiratory distress [3.3 *vs.* 1.2%; $\chi^2$(df = 1) = 7.80; $P$ = 0.005] in women who were thyroid antibody positive.

**Conclusions:** The present study provides further evidence of an association between thyroid antibody positivity and very preterm delivery in euthyroid women. The association with respiratory distress should be considered preliminary and awaits further study. **(*J Clin Endocrinol Metab* 96: E920–E924, 2011)**

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Thyroid antibodies are associated with a number of adverse pregnancy outcomes. In 1990, the presence of thyroid antibodies in unselected euthyroid women in the first trimester of pregnancy was reported to be associated with an increased rate of spontaneous miscarriage (1). Multiple studies since then have confirmed that association (2–4). Women with recurrent abortion, defined as three or more spontaneous miscarriages without an intervening live birth, have also been shown to have an increased rate of thyroid antibodies (5). However, the data on recurrent abortion and thyroid antibody positivity are inconsistent, with some but not all studies demonstrating an association (6). An expanding literature has been exploring the association between thyroid antibody positivity and other negative pregnancy outcomes. In particular, a growing literature has demonstrated an association between thyroid antibodies and preterm delivery, although the findings remain somewhat mixed (7).

In 2005, we began a large-scale randomized trial of levothyroxine therapy in pregnant women in the first trimester of pregnancy who had a TSH above 2.5 mIU/liter and who were thyroid antibody positive. The trial demonstrated a decrease in pregnancy complications as determined by an analysis of a composite outcome consisting of both maternal and neonatal complications (8). A subsequent analysis of the data revealed an increased miscarriage rate in thyroid antibody-negative women with TSH levels between 2.5 and 5.0 mIU/liter (9). The present report compares pregnancy outcome from the 2005 study in women in the first trimester of pregnancy who were euthyroid and thyroid antibody positive to women in the first trimester who were euthyroid and thyroid antibody negative. Because the composite outcome used in our randomized trial has come under criticism, we have focused the present study on the impact of thyroid antibody positivity on individual maternal and neonatal outcomes.

## Subjects and Methods

The present manuscript represents a component of a prospective intervention trial performed in two hospitals in southern Italy, an area of mild iodine insufficiency. Beginning in 2005, 4516 women had sera drawn in the first trimester of pregnancy and were randomly assigned to two groups— universal screening or case finding. The ethical committees of both institutions approved the study, and written informed consent was obtained from all participants. Inclusion criteria included a spontaneous singleton pregnancy and no history of thyroid disease. All women were classified as either high or low risk for thyroid disease. All women in the universal screening group (at both high and low risk for thyroid disease) had their sera immediately tested for TSH, free $T_4$, and thyroid peroxidase. Women in the case-finding group who were at high risk for thyroid disease also had their sera immediately assayed for TSH, free $T_4$, and thyroid peroxidase. Case-finding women who were at low risk for thyroid disease had their sera frozen and evaluated postpartum. Women who were thyroid peroxidase antibody positive and had a TSH exceeding 2.5 mIU/liter were begun on levothyroxine late in the first trimester. Women with a suppressed TSH and an elevated free $T_4$ were referred to an endocrinologist for the management of hyperthyroidism. The primary outcome variable of the 2005 prospective study was a composite of maternal and neonatal complications.

The present study consisted of two groups of women derived from the cohort of 4516 women. We excluded women who had miscarriages (n = 194), women with first-trimester TSH of 2.5 mIU/liter or higher who did not have miscarriages (n = 714), and women who were hyperthyroid and did not have miscarriages (n = 15), leaving 3593 women.

Group A was comprised of 3348 women in the study (irrespective of assignment to universal screening or case finding, or high or low risk for thyroid disease) who were thyroid antibody negative, who had a TSH below 2.5 mIU/liter, and who were not hyperthyroid. Group B was comprised of the 245 women in the study (irrespective of assignment to universal screening or case finding, or high or low risk for thyroid disease) who were thyroid antibody positive, who had a TSH below 2.5 mIU/liter, and who were not hyperthyroid. The two groups were followed prospectively and were compared on a total of 14 maternal or neonatal adverse complications that had been previously reported in the literature to be associated with thyroid disease and pregnancy. Very preterm delivery was defined as a delivery at less than 34 wk gestation (10). The diagnosis of respiratory distress syndrome was based on clinical findings, blood gas analysis, and chest x-ray (11).

Rates of the 14 complications were compared using one-tailed $\chi^2$ (assuming that antibody positivity would never decrease complications). To reduce the error rate associated with multiple comparisons, a per-analysis significance level of 0.007 was selected, based on applying a Bonferroni correction to a one-tailed 0.05 significance level. In addition, the comparisons were repeated, excluding 13 women who were treated with levothyroxine in later trimesters of their pregnancy when they developed hypothyroidism that was detected in either the second or third trimester of pregnancy.

## Results

Table 1 presents demographic information for women in group A (n = 3348) compared with women in group B (n = 245). Women in group B had higher median TSH values than women in group A overall (1.25 *vs.* 0.82; Wilcoxon rank-sum W = 5,903,661; n = 3593; $P < 0.001$). This difference persisted even when excluding women treated with levothiroxine (group A, median, 0.82; range, 0.01–2.49; group B, median, 1.22; range, 0.05–2.48; Wilcoxon rank-sum W = 5,899,662; n = 3580; $P < 0.001$).

Rates of complications across the two groups and overall are shown in Table 2. Two complications were significantly more likely among women who were thyroid antibody positive than among women who were thyroid antibody negative. Antibody-positive women were more likely to have very preterm delivery than antibody-nega-

**TABLE 1.** Characteristics of women analyzed

| | Group A: thyroid antibody negative | Group B: thyroid antibody positive |
|---|---|---|
| n | 3348 | 245 |
| Age (yr), median (IQR, range) | 28 (7, 17–40) | 29 (7, 17–42) |
| Previous babies | 2354 (70) | 172 (70) |
| Smoking | 184 (5.4) | 11 (4.55) |
| 1st gynecological visit (wk), mean (IQR, range) | 9 (2, 3–11) | 9 (2, 3–11) |
| TSH 1st trimester (mIU/liter), median (IQR, range)[a] | 0.82 (1.04, 0.1–2.49) | 1.25 (1.00, 0.05–2.48) |
| FT4 1st trimester (pmol/liter), median (IQR, range) | 12.2 (2.9, 6.1–17.6) | 12.1 (2.7, 6.7–17.3) |
| Family history of thyroid disease | 429 (13) | 32 (13) |
| Goiter | 29 (0.9) | 3 (1.2) |
| Symptoms of hypo-/hyperthyroidism | 259 (7.7) | 17 (6.9) |
| Type 1 diabetes/autoimmune disease | 34 (0.1) | 1 (0.4) |
| Irradiation | 1 (0.0) | 0 (0.0) |
| Previous miscarriage/preterm deliveries | 47 (1.4) | 3 (1.2) |

Women were a subset of participants in Negro *et al.* (8), with hyperthyroid women and women who had miscarriages during their pregnancy excluded. Data are expressed as number (percentage) unless designated otherwise.

[a] $P < 0.05$, Wilcoxon rank-sum test.

tive women [4.5 *vs.* 1.8%; $\chi^2(1) = 8.58$; $P = 0.003$], and their infants were more likely to experience respiratory distress [3.3 *vs.* 1.2%; $\chi^2(1) = 7.80$; $P = 0.005$]. Very preterm delivery and respiratory distress were highly associated [$\chi^2(1) = 696$; $P < 0.001$]. These findings remained significant when women treated later with levothyroxine were excluded [very preterm delivery, 4.7 *vs.* 1.8%; $\chi^2(1) = 9.71$; $P = 0.002$; respiratory distress, 3.4 *vs.* 1.2%; $\chi^2(1) = 8.73$; $P = 0.003$].

## Discussion

The present study compared 14 distinct maternal and neonatal outcomes in women who were thyroid antibody positive in the first trimester of pregnancy to women who were thyroid antibody negative in the first trimester of pregnancy. All women were euthyroid. Each of the 14 adverse outcomes was selected for analysis because prior studies had demonstrated an increase in those complications in pregnant women with thyroid disorders. The size of the present study allowed for each of the 14 adverse outcomes to be evaluated separately, with the primary finding being the significant association between thyroid antibody positivity and the increased rate of very preterm delivery and respiratory distress.

Because TSH elevations have been associated with negative maternal and fetal adverse outcomes, including very preterm delivery, a particular strength of the present study

**TABLE 2.** Rates of complications for euthyroid women with and without thyroid antibodies

| Complication | Overall rate (%) (n = 3593) | Group A: thyroid antibody-negative women (%) (n = 3348) | Group B: thyroid antibody-positive women (%) (n = 245) | *P* |
|---|---|---|---|---|
| Hypertension | 5.6 | 5.6 | 6.1 | 0.740 |
| Preeclampsia | 3.6 | 3.6 | 3.3 | 0.777 |
| Gestational diabetes | 3.8 | 3.8 | 3.3 | 0.659 |
| Cesarean section | 21.0 | 20.9 | 22.4 | 0.560 |
| Preterm labor | 6.0 | 6.0 | 6.5 | 0.723 |
| Respiratory distress | 1.3 | 1.2 | 3.3 | 0.005 |
| NICU admission | 5.3 | 5.3 | 5.3 | 0.994 |
| Low birth weight | 4.9 | 4.8 | 6.5 | 0.229 |
| High birth weight | 5.9 | 5.8 | 7.3 | 0.330 |
| Very preterm delivery | 2.0 | 1.8 | 4.5 | 0.003 |
| Preterm delivery | 4.9 | 4.9 | 2.4 | 0.078 |
| Low Apgar scores | 0.6 | 0.5 | 0.8 | 0.571 |
| Neonatal death | 0.6 | 0.6 | 0.8 | 0.672 |
| Other complications | 0.8 | 0.7 | 0.8 | 0.903 |

Hypertension, Blood pressure above 140/90 mm Hg; preeclampsia, hypertension above 140/90 mm Hg and proteinuria (>300 mg/24 h); gestational diabetes, newly diagnosed and type 1 diabetes; preterm labor, labor before 37 wk; respiratory distress, developmental insufficiency of surfactant production and structural immaturity in the lungs; miscarriage (including still birth), fetal death within 24 wk; NICU, admission to neonatal intensive care unit; low birth weight, ≤2500 g; high birth weight, greater than 4000 g; very preterm delivery, delivery before 34 wk; preterm delivery, delivery 34–37 wk; low Apgar score, ≤3 at 5 min; perinatal/neonatal death, fetal death after 24 wk, and neonatal death up to 7 d.

was the ability to remove the confound of TSH level on adverse outcomes (7). Although it should be noted that TSH levels were minimally but significantly higher in the thyroid antibody-positive group compared with the thyroid antibody-negative group (median TSH, 1.25 *vs.* 0.82 mIU/liter, respectively), it is unlikely that the 0.43 mIU/liter difference between the two groups was clinically significant. Thus, a clear association between thyroid antibody positivity and adverse maternal/neonatal outcomes was demonstrated, even among euthyroid women.

Prior studies on the association between thyroid antibodies and preterm delivery have yielded intriguing results. Three studies reported a significant correlation. Glinoer *et al.* (12) found a doubling in the preterm delivery rate in thyroid antibody-positive Belgian women (16 *vs.* 8%; $P < 0.005$). Ghafoor *et al.* (13) assayed 1500 pregnant Pakistani women for thyroid antibodies and reported that thyroid antibody-positive women had a significantly higher rate of preterm delivery when compared with women who were thyroid antibody negative (26.8 *vs.* 8.0%, respectively; $P < 0.01$). Similarly, in a prospective trial, Negro *et al.* (14) reported a significant increase in preterm delivery in southern Italy in thyroid antibody-positive women when compared with women who were thyroid antibody negative (22.4 *vs.* 8.2%). On the other hand, a retrospective study by Tierney *et al.* (15) performed in Australia found no difference in preterm delivery between women who were thyroid antibody positive and women who were thyroid antibody negative. Likewise, in a nested case-control study performed in New Jersey, Stagnaro-Green *et al.* (16) reported a similar rate of thyroid antibody positivity in women who delivered at term when compared with women with preterm delivery. Finally, three studies, all published in either 2009 or 2010, found no association between thyroid antibody status and preterm delivery, but each reported a significant increase in an adverse perinatal outcome in women who were thyroid antibody positive. Männistö *et al.* (17) found an increase in perinatal death, Haddow *et al.* (18) reported an increase in preterm premature rupture of membranes, and Abbassi-Ghanavati *et al.* (19) reported a 3-fold increase in placental abruption. Based on a review of these eight studies, in combination with the present findings, it could be concluded that thyroid antibody positivity is associated with adverse perinatal outcomes.

To our knowledge, there have been no prior reports of an association between thyroid antibodies and respiratory distress. In a prospective observational study performed in Texas, Casey *et al.* (20) reported that respiratory distress was twice as common in infants born to mothers diagnosed with subclinical hypothyroidism during pregnancy. Thyroid antibody status of the women was not reported at that time, but subsequent analysis of the same cohort failed to find an association between thyroid antibody positivity and respiratory distress (19). Although it is feasible that the relationship found in the present study is merely a chance association, it should be noted that the level at which a finding was considered significant was modified to a $P < 0.007$ to take into account the impact of multiple comparisons. Nevertheless, the positive association reported between thyroid antibody positivity and neonatal respiratory distress should be interpreted as preliminary and in need of confirmation.

In conclusion, the present study provides further evidence of an association between thyroid antibody positivity and very preterm delivery and reports the novel finding of a link between neonatal respiratory distress and the presence of thyroid antibodies. Strengths of the present study include the overall number of women studied and controlling for TSH, which has been previously reported to be associated with very preterm delivery. Weaknesses of the study are the homogeneity of the population, which consisted of women in southern Italy, an area of mild iodine deficiency. A large prospective trial of levothyroxine therapy in thyroid peroxidase-positive euthyroid women is warranted.

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