**SUMMARY**

**Context:** Euthyroid women with autoimmune thyroid disease show impairment of thyroid function during gestation and seem to suffer from a higher rate of obstetrical complications.

**Objective:** The authors sought to determine whether these women suffer from a higher rate of obstetrical complications and whether l-T4 treatment exerts beneficial effects.

**Design:** This was a prospective study.

**Setting:** The study was conducted in the Department of Obstetrics and Gynecology.

**Patients:** A total of 984 pregnant women were studied from November 2002 to October 2004; 11.7% were thyroid peroxidase antibody positive (TPOAb(+)).

**Intervention:** TPOAb(+) patients were divided into two groups: group A (n = 57) was treated with LT(4), and group B (n = 58) was not treated. The 869 TPOAb(-) patients (group C) served as a normal population control group.

**Main Outcome Measures:** Rates of obstetrical complications in treated and untreated groups were measured.

**Results:** At baseline, TPOAb(+) had higher TSH compared with TPOAb(-); TSH remained higher in group B compared with groups A and C throughout gestation. Free T4 values were lower in group B than groups A and C after 30 wk and after parturition. Groups A and C showed a similar miscarriage rate (3.5 and 2.4%, respectively), which was lower than group B (13.8%) [P < 0.05; relative risk (RR), 1.72; 95% confidence interval (CI), 1.13-2.25; and P < 0.01; RR = 4.95; 95% CI = 2.59-9.48, respectively]. Group B displayed a 22.4% rate of premature deliveries, which was higher than group A (7%) (P < 0.05; RR = 1.66; 95% CI = 1.18-2.34) and group C (8.2%) (P < 0.01; RR = 12.18; 95% CI = 7.93-18.7).

**Conclusions:** Euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with l-T4 is able to lower the chance of miscarriage and premature delivery.
Usefulness of l-T4 administration in euthyroid pregnant women with thyroid autoantibodies.

A group of 984 euthyroid pregnant women with thyroid autoantibodies (TPO-Abs) was investigated with the aim to assess whether these women would benefit from l-T4 administration to improve pregnancy outcome and reduce the rates of miscarriage and premature delivery.

Measurements of TPO-Abs and thyroid function tests were carried out at the first prenatal visit, repeated at 20 and 30 weeks of gestation and 3 days after delivery. One hundred and fifteen women (11.7%) were shown to have positive thyroid autoantibodies (‘TAI positive’). An interesting observation was that TAI-positive women were significantly older than the control population.

TAI-positive women were randomly assigned to group A (who received l-T4) or group B (with no treatment). TAI-negative women served as controls. The trial design was randomized and prospective, but not placebo-controlled and not double-blind, and the medical participants to the study were kept unaware of the group to which patients belonged. A remarkable feature of this study was that TAI-positive women were significantly older than the control population.

Serum TSH levels also increased progressively in the control group but much less, from 1.1 to 2.1 µU/ml at term, as a result of mild iodine deficiency in this population. Not only was the spontaneous serum TSH increment quantitatively significantly less marked in controls, compared with group B women, but also the control and group A (treated) women were able to maintain normal serum free T4 levels, whereas serum free T4 levels decreased by 30% during gestation in group B women, as a consequence of the reduced functional thyroid reserve associated with chronic thyroiditis.

The most novel and important result of present study was that l-T4 administration allowed for a significant decrease in the rate of obstetrical complications. The miscarriage rate was reduced by 75% and the frequency of premature delivery by 69%. These results confirm data produced previously by other investigators who have shown an association between thyroid autoimmunity and adverse obstetrical outcome, even in the absence of thyroid dysfunction. Their importance is that for the first time in a prospective randomized study, a clear benefit of l-T4 administration was shown on the outcome of pregnancy in women with thyroid autoimmunity and without evident perturbation of thyroid function in early gestation.

An association between the risk of a miscarriage and autoimmune thyroid disease (AITD) was first reported 15 years ago and the statistical strength of this association has been largely confirmed in several population studies. AITD - without overt thyroid dysfunction - is associated
with a 3- to 5-fold increase in overall miscarriage rate. In a recent meta-analysis of all case-controlled and longitudinal studies published since 1990, the overall relative risk of miscarriage was confirmed to be increased by approximately 3-fold in women with AITD.

Finding an association does not imply a causal relationship, and the aetiology of an increased pregnancy loss in women with AITD remains largely unknown. Three hypotheses have been proposed. The first hypothesis holds that pregnancy loss is not directly related to the presence of circulating thyroid antibodies. In this view, AITD could represent only a marker of an underlying more generalized autoimmune imbalance that, in turn, would explain a greater rejection rate of the foetal graft. The second hypothesis holds that the presence of AITD could be associated with a subtle deficiency in thyroid hormone concentrations or a lesser ability of thyroid function to adapt adequately to the changes associated with the pregnant state because of a reduced thyroid functional reserve characteristic of chronic thyroiditis. The third hypothesis holds that AITD could act by delaying the occurrence of conception because of its known association with infertility. Thus, TAI-positive women tend to become pregnant at an older age (3-4 years older, on the average) and older women are more prone to pregnancy loss. These hypotheses do not contradict one another, and it remains plausible that the increased risk of pregnancy loss associated with AITD is multi-factorial, eventually resulting from a combination of several independent deleterious factors. If underlying mild thyroid deficiency plays a role to explain increased pregnancy loss, this would constitute a strong argument to screen systematically women for thyroid antibodies or mild thyroid insufficiency (before conception when they express the desire of being pregnant or as soon as a pregnancy has started) and give them the potential benefit of l-T4 treatment.

Until the present study, only three other studies have investigated whether a medical intervention would benefit women with thyroid autoimmunity. In a study by Vaquero in 2000, TAI-positive women with 2 previous first-trimester miscarriages were subdivided into women who received iv immunoglobulins during pregnancy and women who received dessicated thyroid extracts before conception and during pregnancy. Pregnancy success rate was 81% in the l-T4 group, compared with 55% in the IgG group. Negro et al. in 2005 reported the results of l-T4 administration in euthyroid TAI-positive infertile women undergoing IVF. The miscarriage rate was reduced to 33% compared with 52% in the untreated controls, but the study failed to reach statistical significance. Finally in a slightly different clinical setting, a study by Abalovich et al. in 2000 showed that it was not so much the diagnosis of overt versus subclinical hypothyroidism that mattered in relation with the outcome but mainly the adequacy of l-T4 treatment. Pregnancy outcome was compared in 27 hypothyroid women who received an adequate l-T4 treatment with 24 hypothyroid women in whom the treatment was not adequately adjusted during gestation. In pregnant women with an adequate treatment, the frequency of abortions was minimal and pregnancies carried to term without complications, while in the women with an inadequate treatment, pregnancy ended with abortion in 60-71% of the women.
What are the main lessons to be learned from present study? First, it confirmed previously known findings, namely that euthyroid women with thyroid antibodies tend to be older when becoming pregnant; that even though euthyroid in early gestation, these women tend to have a reduced thyroid functional reserve; that they have an increased risk for obstetrical complications such as miscarriage and premature delivery; and finally that when given the benefit of treatment with thyroid hormone, they normalize thyroid function and behave normally. Furthermore, the study clearly showed the benefits of l-T4 administration in pregnant women with AITD, not only to correct maternal thyroid function but also to reduce markedly the rate of undesired obstetrical events and lower their prevalence down to that found in healthy controls. There is no reason to believe that l-T4 played a role in altering underlying autoimmunity. Also, the age difference between TAI-positive and controls was not large enough to explain the different rates of miscarriage and premature birth (and even less changes in these rates after l-T4 treatment). Present study therefore leads us to conclude that among the three hypotheses evoked above, the second one, i.e. a subtle deficiency in thyroid hormone concentration and/or a lesser ability of maternal thyroid function to adapt adequately in women with AITD, was the main reason for the beneficial effects of thyroid hormone administration. If confirmed by future studies, these results would constitute an additional argument to screen pregnant women systematically for the presence of asymptomatic chronic autoimmune thyroiditis and/or mild thyroid underfunction to give such women the benefit of thyroid hormone treatment.

(Extracts from the Editorial (JCEM) to the article written by Daniel Glinoer, MD; PhD)