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Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications

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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: We sought to determine whether these women suffer from a higher rate of obstetrical complications and whether levothyroxine (LT_4) 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 T_4 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 LT_4 is able to lower the chance of miscarriage and premature delivery. (***J Clin Endocrinol Metab* 91: 2587–2591, 2006**)

THYROID AUTOIMMUNITY (TAI) appears to be a determining factor in pregnancy loss. Many studies have confirmed this association, not only in hypo- and hyperthyroid women but also in euthyroid ones (1–3). Three hypotheses have been cited to explain this association: 1) thyroid antibodies may represent a marker of a generalized autoimmune imbalance that is responsible for an increased miscarriage rate; 2) despite laboratory euthyroidism, women who are positive for thyroid antibodies before pregnancy may develop subclinical or overt hypothyroidism during pregnancy because a preexisting subtle thyroid dysfunction may worsen during pregnancy (in particular during the first trimester); and 3) because TAI represents a risk factor for infertility, women with antibodies are often older than those without, so an older age, *per se*, may explain the increased rate of fetal loss.

Another matter of concern is the relationship between thyroid function and obstetrical complications. Several studies confirmed that not only is overt hypothyroidism associated with maternal and fetal adverse consequences, but also subclinical hypothyroidism or euthyroidism in patients affected by TAI may adversely affect the mother or fetus (4–8). Additionally, unfavorable obstetric events appear to be more frequent when hypothyroidism is diagnosed too late and/or when the levothyroxine (LT_4) replacement is not adequate to ensure euthyroidism during pregnancy (7). The dual aims of the present study are to assess whether euthyroid women positive for thyroid peroxidase antibodies ($TPOAb^+$) are affected by a higher rate of obstetrical complications and to explore the hypothesis that LT_4 treatment may improve the outcome of affected patients.

Subjects and Methods

A total of 1074 Caucasian pregnant women who attended the Department of Obstetrics and Gynecology were screened for TPOAb. Levels of TSH and free T_4 (FT_4) were also determined. The study was carried out from November 2002 to October 2004. Forty-five of 1074 (4.2%) women were excluded for overt hypo- or hyperthyroidism or for preexisting thyroid dysfunction. A total of 1029 women participated in the study, and 984

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Abbreviations: CI, Confidence interval; FT_4, free T_4; LT_4, levothyroxine; RR, relative risk; TAI, thyroid autoimmunity; TPOAb, thyroid peroxidase antibodies.

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completed it. TPOAb titers were checked and thyroid function tests were performed at the first gynecological visit, at 20 and 30 wk gestation, and 3 d after delivery. One hundred fifteen of 984 (11.7%) subjects were $TPOAb^+$. The 115 $TPOAb^+$ women were divided into two groups, an intervention group (group A, n = 57) treated with LT_4 and another group (group B, n = 58) without treatment. The $TPOAb^-$ women (group C, n = 869) served as a normal control group. In group A, the patients treated with LT_4 received a dose of 0.5 μg/kg·d if they had TSH less than 1.0 mIU/liter, 0.75 μg/kg·d for TSH between 1.0 and 2.0 mIU/liter, and 1 μg/kg·d for TSH higher than 2.0 mIU/liter or a TPOAb titer exceeding 1500 kIU/liter. These dosages were maintained throughout gestation.

LT_4 administration was started on the first endocrinological visit, which occurred 3–7 d after the first gynecological visit. A computer program was used to randomly assign the $TPOAb^+$ patients to either group A or group B. A sealed opaque envelope was assigned to each patient; only the doctor treating the patient, who did not participate in any subsequent phase of the study, knew which group the patient was in. Medical doctors participated in different phases of the protocol, so that each was unaware of which group the patients belonged to. If hyperthyroidism was observed, the patient was excluded from the study protocol.

Obstetrical complications were classified as follows. Gestational hypertension was defined as an intrapartum systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg. Severe preeclampsia was diagnosed in women with hypertension who had at least one of the following: blood pressure higher than 160/110 mm Hg, serum creatinine greater than 1.0 mg/dl, a platelet count less than 100,000/μl, serum aspartate aminotransferase level at least twice the normal value, persistent headache or scotomata, 2+ or greater proteinuria, or more than 2 g protein excreted in 24 h. A birth before 37 wk gestation was considered to be a preterm birth.

Serum TSH and FT_4 were measured using a third-generation electrochemiluminescence immunoassay (Roche, Basel, Switzerland). The reference values were 0.27–4.2 mIU/liter for TSH and 9.3–18.0 ng/liter (12–33.5 pmol/liter) for FT_4. Intra- and interassay coefficients of variation were 2.4 and 9.5% for TSH and 4.7 and 6.9% for FT_4. TPOAb titers were determined using a RIA kit (Brahms Diagnostica, Berlin, Germany). The reference range was 0–100 kIU/liter. TPOAb titers of more than 100 kIU/liter were considered positive.

Statistical analysis was performed using an SPSS (SPSS, Inc., Chicago, IL) program, by means of Fisher's exact test. Correlations between variables were assessed using Spearman's test, and differences between mean values were determined by the Mann-Whitney *U* test. A multivariate approach was used, starting with a univariate model for each individual variable. Mean TSH values were calculated after log transformation. All statistical tests were considered statistically significant whenever $P < 0.05$.

This study was conducted in accordance with guidelines in the Declaration of Helsinki. The Institutional Review Board approved the study protocol, and all the participants gave a written informed consent.

Results

The age range was 17–38 yr, with a Gaussian distribution (mean ± SD, 29 ± 5 yr). The average age of group C was significantly lower than groups A and B taken together: 28 ± 5 *vs.* 30 ± 6; $P < 0.05$. The first endocrinological visit took place at gestational wk 10.4 ± 3.1 in group A, at wk 10.3 ± 3.1 in group B, and at wk 10.4 ± 3.3 in group C (mean ± SD) (Table 1). Ninety-two percent of the women consulted the endocrinologist before the 20th wk of gestation (Fig. 1, *top*).

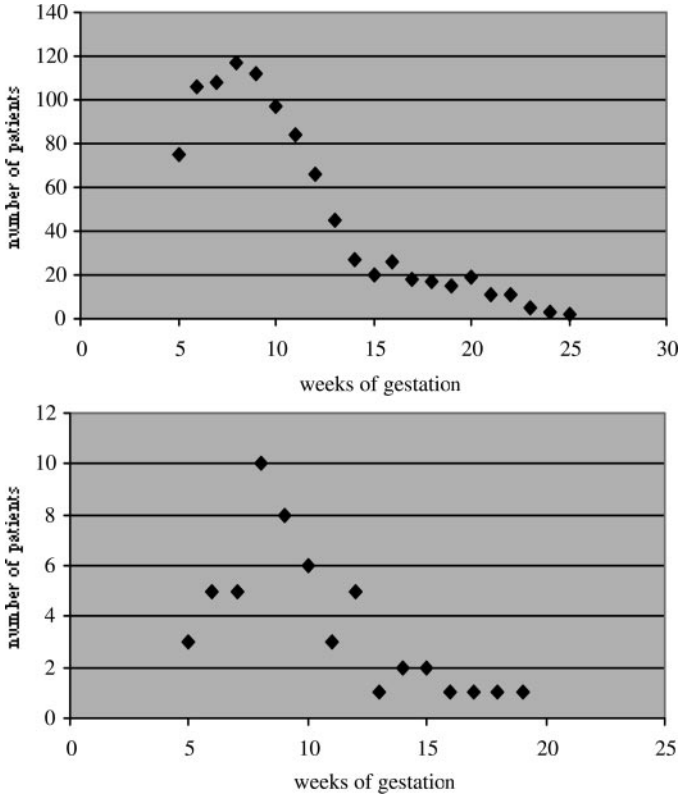

FIG. 1. Gestational time of the first endocrinological visit for all patients participating in the study (*top*) and for group A ($TPOAb^+$ treated with LT_4) (*bottom*).

The LT_4 administered in group A was 49.7 ± 14 μg/d; eight patients received 0.5 μg/kg·d (30.6 ± 4.9 μg/d), 35 received 0.75 μg/kg·d (47.7 ± 6.0 μg/d), and 14 received 1 μg/kg·d (64.7 ± 8.7 μg/d). When the LT_4 treatment was started, the gestational ages were similar in the three subgroups submitted to the three different dosages (9.6 ± 5, 10.1 ± 3.7, and 10.9 ± 3.8 wk, respectively). In group A, 23 of 45 patients (40%) started LT_4 treatment by the 8th week and 45 (79%) by the 12th week (Fig. 1, *bottom*).

Thyroid function tests

Whether they had extremely or moderately elevated TPOAb titers, women in groups A and B showed a 62% decrease in TPOAb titers at delivery compared with the initial values.

Initially, the mean TSH values were significantly higher in groups A and B compared with group C (1.6 ± 0.5 and 1.7 ± 0.4, respectively, *vs.* 1.1 ± 0.4 mIU/liter; $P < 0.05$ and $P < 0.05$, respectively). In group A, TSH baseline values were significantly different between the three subgroups given 0.5, 0.75, and 1.0 μg/kg·d dosages of LT_4 (0.7 ± 0.2, 1.4 ± 0.3, and

TABLE 1. Characteristics of patients at 10, 20, and 30 wk gestation and delivery (D)

			TSH (mIU/liter)				FT_4 (ng/liter)			
	n	Age (yr)	10 wk	20 wk	30 wk	D	10 wk	20 wk	30 wk	D
$TPOAb^+$ LT_4	57	30 ± 5	1.6 ± 0.5	1.1 ± 0.4	1.2 ± 0.4	1.9 ± 0.5	14.8 ± 4.2	14.2 ± 3.8	14.3 ± 3.6	14.3 ± 3.2
$TPOAb^+$	58	30 ± 6	1.7 ± 0.5	2.3 ± 0.5	2.5 ± 0.6	3.5 ± 0.7	14.6 ± 4.3	13.8 ± 4.8	12.4 ± 4.9	10.2 ± 4.5
$TPOAb^-$	869	28 ± 5	1.1 ± 0.4	1.2 ± 0.4	1.4 ± 0.4	2.1 ± 0.6	15.2 ± 4.1	14.3 ± 4.0	13.8 ± 4.2	14.6 ± 3.8

Data are expressed as mean ± SD.

2.6 ± 0.7 mIU/liter; $P < 0.01$). However, at 20 and 30 wk gestation and after parturition, TSH values were similar in the three subgroups (Fig. 2). The TSH values of group B remained significantly higher than those of groups A and C during the entire gestation period, with a sharp increase at parturition (3.5 ± 0.7 mIU/liter; $P < 0.01$). At delivery, 19% of group B showed a TSH value higher than the normal range (Fig. 3, *top*).

FT_4 baseline values were similar in groups A and B, but these groups had FT_4 values lower, although not significantly, than group C. At 30 wk gestation, FT_4 values were lower in group B than groups A and C ($P < 0.01$ and $P < 0.01$, respectively), with a marked decrease in group B after delivery, when 53% of cases showed FT_4 values under the normal range (Fig. 3, *bottom*).

The differentiated LT_4 dosages assigned on the basis of the TSH starting values thus allowed us to obtain, in the intervention group (group A), TSH and FT_4 values that were not significantly different from the normal control group (group C).

Obstetrical complications

Group A and group C had a similar miscarriage rate (3.5 and 2.4%, respectively), whereas group B was characterized by a higher percentage of pregnancy loss (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] (Fig. 4, *top*). The difference in miscarriage rates was a result of patients who miscarried within the first trimester of pregnancy; in fact, in groups A and B, all the miscarriages occurred within the first trimester, and in group C, 19 of 21 miscarriages occurred during the first trimester. Consequently, we conclude that LT_4 treatment could not significantly influence the miscarriage rate, if given after 12 wk. The two pregnancy losses observed in group A occurred at 7 and 10 wk gestation (both pregnant women were on LT_4). One of the eight pregnancy losses observed in group B occurred at 6 wk, two at 7 wk, three at 8 wk, and one each at 10 and 11 wk gestation. In group C, two of 21 pregnancy losses occurred at 6 wk, five at 7 wk, eight at 8 wk, two at 10 wk, and one each at 11, 12, 16, and 21 wk gestation. Group B presented a higher number of premature deliveries (22.4%) compared with 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) (Fig. 4, *bottom*). Thus, the LT_4 treatment appeared to be effective in reducing miscarriages whether given before or after the first trimester of pregnancy. Other obstetrical complications (*i.e.* hypertension, preeclampsia, and placental abruption) (Table 2) and the clinical characteristics of newborns (weight, height, cranial perimeter, and APGAR score) did not vary between groups.

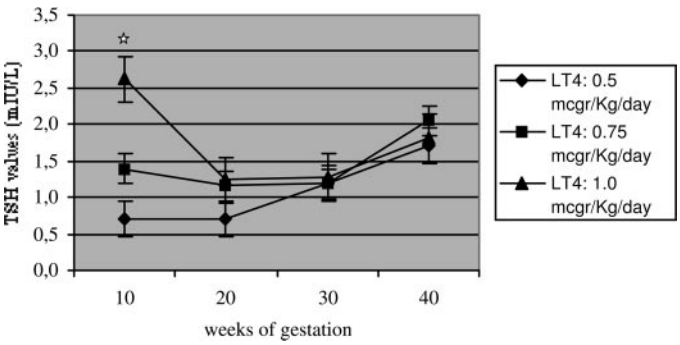

FIG. 2. TSH trends in the three subgroups treated with different dosages of LT_4 on the basis of their initial TSH values.

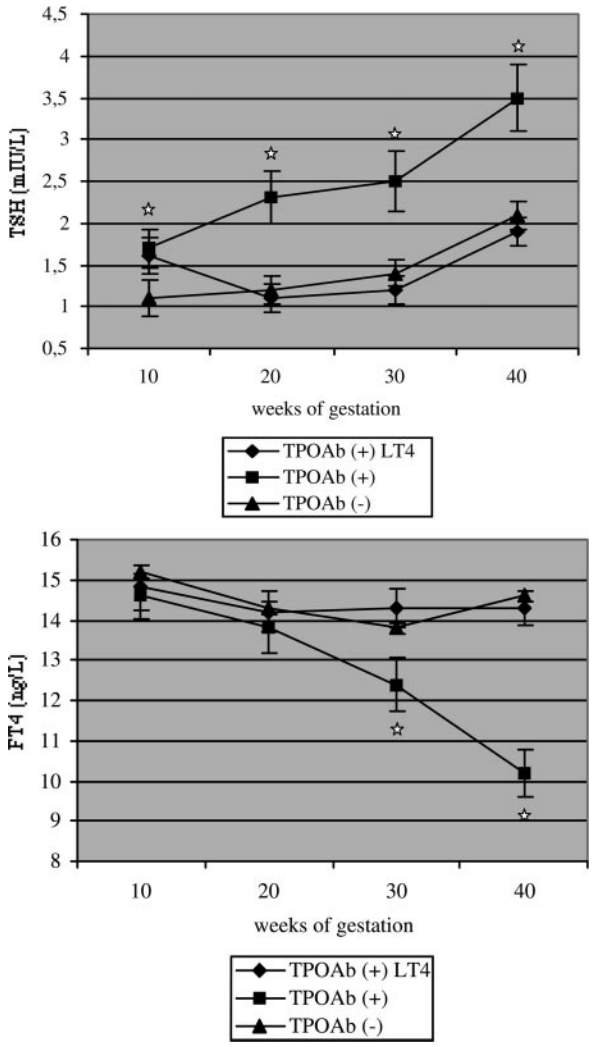

FIG. 3. *Top*, TSH values during gestation in group A ($TPOAb^+$ treated with LT_4), group B ($TPOAb^+$), and group C ($TPOAb^-$). At 10 wk, groups A and B were higher than group C; at 20 and 30 wk and after delivery, groups A and C were lower than group B. *Bottom*, FT_4 values during gestation. At 30 wk and after delivery, groups A and C were higher than group B. ☆, $P < 0.05$.

Discussion

In this study, we analyzed the outcome of three groups of euthyroid pregnant women. Subjects positive for TPOAb were divided into two groups, one that was given LT_4 treatment; the third group was composed of pregnant women who were $TPOAb^-$. The aims were to assess whether $TPOAb^+$ pregnant women showed an increased percentage of obstetrical complications in comparison with those without antibodies and whether the LT_4 treatment had some beneficial effects on these events.

The prevalence of TAI in our population was 11.7%, a percentage that is in agreement with the data found in other studies

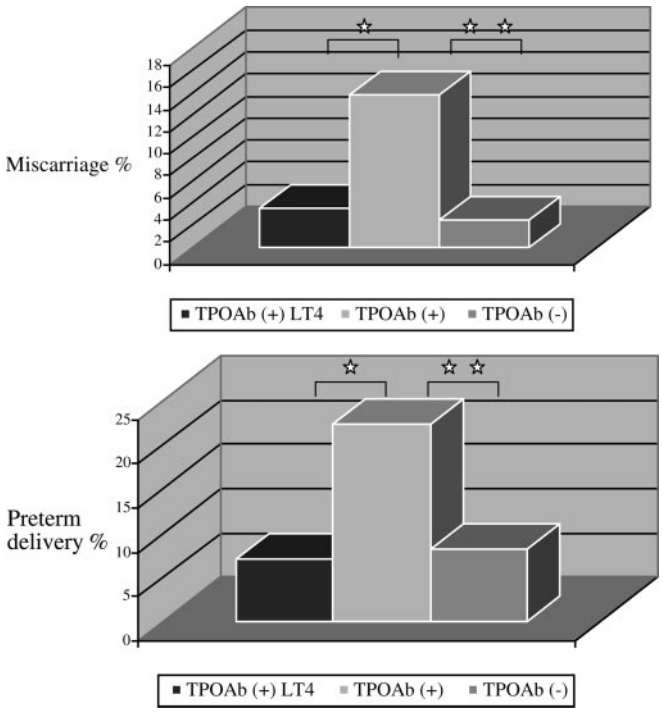

FIG. 4. Percentage of miscarriages (*top*) and premature deliveries (*bottom*) in group A ($TPOAb^+$ treated with LT_4), group B ($TPOAb^+$), and group C ($TPOAb^-$). ☆, $P < 0.05$; ☆ ☆, $P < 0.01$.

(1, 8, 9). Furthermore, the average age of women affected by TAI was slightly, but significantly, older than the unaffected group; this finding indirectly confirms that the presence of thyroid antibodies is associated with reduced fertility. One proposed hypothesis to explain the association of TAI with an increase in miscarriages is that TAI represents a risk factor for subfertility, delaying pregnancy in women with TAI; thus, when women with TAI do become pregnant, they are older and face a higher risk of pregnancy loss (10, 11).

At the beginning of their pregnancy, women with TAI showed a higher TSH level compared with those who were $TPOAb^-$, although the mean TSH level was still within the normal range. As previously demonstrated, these subjects are prone to developing subclinical or overt hypothyroidism during pregnancy (8). In these cases, the thyroid fails to adapt its function to the increased hormone requirement (12). Although it is not currently recommended to start LT_4 treatment in TAI, pregnancy may represent a difficult challenge for the thyroid. We noted that after parturition, about half of the patients in this study had FT_4 values below the minimal limit. Therefore, this study confirms that a thyroid with a reduced functional reserve does not compensate for the increased hormone requirement caused by high thyroid-binding globulin concentrations, increased volume distribution of thyroid hormones, and increased placental T_4 transport and degradation (13). In the $TPOAb^-$ group (group C), TSH values increased from 1.1 mIU/liter at 10 wk gestation to 2.1 mIU/liter at term. The spontaneous increment in serum TSH was, however, quantitatively and significantly less than the one observed in group B (untreated $TPOAb^+$ group). Concerning the adaptation of thyroid function during pregnancy, it has to be taken into account that this study was conducted in Italy, a country that is still characterized by iodine deficiency, because iodized salt is not compulsory by law. On the basis of the results of this study, we speculate that the tendency of hypothyroxinemia in healthy pregnant women presents a strong stimulus for the pituitary to compensate, with a subsequent rise in TSH values.

TABLE 2. Pregnancy outcome

Pregnancy complications	Group A $TPOAb^+$ LT_4 (n = 57)	Group B $TPOAb^+$ (n = 58)	Group C $TPOAb^-$ (n = 869)
Hypertension	5 (8.8)	7 (12)	63 (7.2)
Preeclampsia	2 (3.5)	3 (5.2)	32 (3.7)
Placental abruption	0	1 (1.7)	4 (0.5)
Miscarriage	2 (3.5)	8 (13.8)	21 (2.4)
Preterm delivery	4 (7)	13 (22.4)	71 (8.2)

Numbers in parentheses represent percentage.

The development of hypothyroidism can generally be predicted at the beginning of pregnancy on the basis of the TSH value and TPOAb titers, so that patients displaying TSH more than 2.0 mIU/liter and/or high TPOAb (>2000 kIU/liter) are more likely to develop overt thyroid dysfunction (8). A secondary endpoint of the present study was to fine tune the LT_4 replacement dose and develop, if possible, practical suggestions on how to treat patients at risk of developing hypothyroidism. In fact, the subgroups given three different dosages of LT_4 showed a significant difference initially in baseline TSH values that was abolished during gestation. From the data, we can say that the assigned LT_4 dose made it possible to maintain the $TPOAb^+$ women in a euthyroid state, with TSH and FT_4 values that were similar to the ones showed by the $TPOAb^-$ group.

The development of thyroid dysfunction during pregnancy can cause complications. It has been already demonstrated that both overt and subclinical hypothyroidism are associated with obstetrical repercussions. Maternal complications include anemia, postpartum hemorrhage, cardiac dysfunction, preeclampsia, and placental abruption; fetal complications include fetal distress, premature birth, and/or low birth weight, congenital malformations, and fetal/perinatal death (4–8, 14). In our study population sample, treatment with LT_4 had a positive effect on reducing the rates of miscarriages and premature delivery. In fact, this group of patients had a significantly reduced risk of miscarriage compared with the $TPOAb^+$ patients who were not treated with LT_4, and LT_4 treatment reduced the miscarriage rate to a value comparable to that of the $TPOAb^-$ patients. Comparing premature delivery rates, the beneficial intervention with LT_4 reduced preterm births in $TPOAb^+$ women to a percentage similar to that of the control population. Timing of treatment initiation appears to be of critical importance. In fact, the LT_4 treatment turned out to be extremely effective in reducing the number of miscarriages when given during the early stages of pregnancy, because miscarriages generally occurred within the first trimester. On the other hand, the rate of premature deliveries was also significantly reduced in women whose LT_4 treatment was started after the first trimester. This allows us to speculate that euthyroxinemia is primarily important in early pregnancy to avoid miscarriages and to maintain normal placental development and function throughout gestation to avoid preterm deliveries.

From the data we observed, we cannot definitively exclude the possibility that the increased miscarriage rate found in $TPOAb^+$ women may be partly because of their older age. The age difference between $TPOAb^+$ and $TPOAb^-$ patients was just

2 yr; therefore, we cannot state that, also with a greater age difference, LT_4 is able to, as such, reduce pregnancy loss. Another question is whether TAI is an indicator of an unfavorable autoimmune environment. In a recent study carried out in infertile women undergoing assisted reproduction technologies, a lower delivery rate was found in $TPOAb^+$ compared with $TPOAb^-$. However, in that study, LT_4 treatment was not found to be beneficial (15). Taking this into consideration, we can speculate that the difference between women undergoing assisted reproduction technologies and the patients examined in this paper is that the populations had differences in fertility. In other words, autoimmunity in infertile women, (with not only TPOAb, but also antiphospholipid and antinuclear antibodies, for example) may play a major role in fertilization, implantation, and placental development, so that LT_4 treatment alone is not effective. Conversely, in fertile women, as in this study, TAI alone may play a lesser role, and the advantageous effects of LT_4 become more evident. Then, although we cannot exclude the influence of age and autoimmunity on obstetrical complications, on the other hand we can confirm that euthyroid pregnant women affected by autoimmune thyroid disease are inclined to develop thyroid dysfunction during gestation.

The $TPOAb^+$ women not treated with LT_4 had, as a group, lower FT_4 values compared with the other two groups. Considering the fact that basal TSH concentrations in the upper reference range are often associated with subnormal thyroid function, the $TPOAb^+$ women in this study displayed relatively reduced thyroid hormone values (16). There are two undesirable consequences to having low or low-normal FT_4 values, the risk of obstetrical complications and the risk of altered fetal brain development. Up to midgestation, when the fetal thyroid begins to work, early fetal brain development depends exclusively on the availability of FT_4 in embryonic and fetal tissues; thus, during early gestation, maternal euthyroxinemia appears to be critical for normal fetal brain development (17). Every effort must be made to detect and prevent early maternal hypothyroxinemia to prevent neurodevelopmental defects, which may include an increased chance of lower IQ and a higher risk of cerebral palsy, (18, 19). Furthermore, reports of poor development in many babies faced with premature interruption of the maternal supply of thyroid hormone, occurring when the thyroid is still immature, also indicate that the fetal brain needs thyroid hormones throughout the whole gestation period and that an adequate supply of maternal T_4 has an important protective role after midgestation (20). Therefore, as a final thought about thyroid function, in this context, not only TSH but also FT_4 needs to be monitored and promptly adjusted throughout the entire gestation period. Impaired thyroid function is associated with an increased risk of miscarriage and premature deliveries; a substitutive treatment with LT_4 is able to compensate for the reduced thyroid function reserve, lowering the chance of miscarriage and premature deliveries.

To our knowledge, this is the first study that clearly shows the benefits of LT_4 administration, not only to correct maternal thyroid function but also to decrease the rate of undesired obstetrical events and bring their prevalence down to those of the control population. Our results lead us to agree with Poppe and Glinoer (21), who recommend screening women early in pregnancy for TPOAb and for thyroid function. We also agree with their recommendation of administering LT_4, at least, to women who have a TSH value greater than 2.0 mIU/liter and/or a high titer of thyroid antibodies.

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