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The Influence of Selenium Supplementation on Postpartum Thyroid Status in Pregnant Women with Thyroid Peroxidase Autoantibodies

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Context: Pregnant women who are positive for thyroid peroxidase antibodies [TPOAb(+)] are prone to develop postpartum thyroid dysfunction (PPTD) and permanent hypothyroidism. Selenium (Se) decreases thyroid inflammatory activity in patients with autoimmune thyroiditis.

Objective: We examined whether Se supplementation, during and after pregnancy, influences the thyroidal autoimmune pattern and function.

Design: This was a prospective, randomized, placebo-controlled study.

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

Patients: A total of 2143 euthyroid pregnant women participated in the study; 7.9% were TPOAb(+).

Interventions: During pregnancy and the postpartum period, 77 TPOAb(+) women received selenomethionine 200 μg/d (group S1), 74 TPOAb(+) women received placebo (group S0), and 81 TPOAb(−) age-matched women were the control group (group C).

Main Outcome Measures: We measured the prevalence of PPTD and hypothyroidism.

Results: PPTD and permanent hypothyroidism were significantly lower in group S1 compared with S0 (28.6 *vs.* 48.6%, $P < 0.01$; and 11.7 *vs.* 20.3%, $P < 0.01$).

Conclusion: Se supplementation during pregnancy and in the postpartum period reduced thyroid inflammatory activity and the incidence of hypothyroidism. (***J Clin Endocrinol Metab* 92: 1263–1268, 2007**)

THE STATE OF PREGNANCY represents a functional challenge for the thyroid gland (1). In particular, women positive for thyroid peroxidase antibodies [TPOAb(+)] are prone to develop hypothyroxinemia during pregnancy and thyroid dysfunction after delivery (2). An autoimmune destructive process characterized by elevated TPOAb causes postpartum thyroiditis (PPT), which occurs during the first postpartum year. PPT is an exacerbation of an underlying autoimmune thyroiditis, which is aggravated by the immunological rebound that follows the partial immunosuppression induced by pregnancy (3, 4). About 50% of TPOAb(+) pregnant women have PPT develop, and among these, more than 40% are affected by permanent hypothyroidism that develops in subsequent years. Factors predictive of thyroid dysfunction include a hypothyroid form of postpartum thyroid disease, high TSH values, and high TPOAb titers (5).

The trace element selenium (Se) plays an important role in the thyroid gland under normal physiological conditions and in disease. Se exerts multiple actions on endocrine systems by modifying the expression of at least 30 selenoproteins, many of which have clearly defined functions. Well-characterized selenoenzyme families include the glutathione peroxidases (GPx), thioredoxin reductases, and iodothyronine deiodinases. These selenoenzymes influence cell function by acting as antioxidants, and modifying redox status and thyroid hormone metabolism (6). Se supplementation may decrease inflammatory activity in patients with autoimmune thyroiditis, especially in those with high activity, and ameliorates the thyroid echogenicity pattern (7, 8). The reduction in TPOAb titers seems to be quite strictly correlated with the amount of Se administered (9). Se is effective in reducing TPOAb titers in patients affected by thyroid autoimmune diseases, probably due to its modification of the inflammatory and immune responses. Given that TPOAb(+) pregnant women are at high risk for an exacerbation of thyroiditis after delivery developing (and permanent hypothyroidism in the following years) and that Se has antiinflammatory activity, it is reasonable to think that Se supplementation in this high-risk population may improve the outcome of thyroid diseases. Because no data are available, we evaluated the in-

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Abbreviations: FT_4, Free T_4; GPx, glutathione peroxidases; LT_4, levothyroxine; PPT, postpartum thyroiditis; PPTD, postpartum thyroid dysfunction; Se, selenium; TPOAb, thyroid peroxidase antibodies; US, ultrasound.

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fluence of Se supplementation on postpartum thyroid status in TPOAb(+) pregnant women.

Subjects and Methods

Participants

The participants included 2227 Caucasian pregnant women recruited from the Department of Obstetrics and Gynecology who were screened for TSH, FT_4, and TPOAb at the first gynecological visit. From 3–5 d later, patients underwent an endocrinological visit with the results of the thyroid function tests. In all, 84 (3.8%) women were excluded for having thyroid dysfunction (already known: 2.4%, or newly diagnosed: 1.4%) or being treated with drugs that interfere with thyroid function. Of the 2143 euthyroid women, 7.9% were TPOAb(+). The 169 euthyroid, TPOAb(+) pregnant women with were randomly divided into two groups: group S1 (85 women), designed to receive selenomethionine 200 μg/d; and group S0 (84 women), designed to receive placebo. In addition, 85 TPOAb(−) age-matched women were recruited as the control group (group C). Either selenomethionine or placebo was started not before 12 wk gestation. All the participants were advised to use iodized salt; iodization of salt is not compulsory by law in Italy. Thyroid tests were performed at 20 and 30 wk gestation and at delivery; after delivery, tests were performed at months 1–2, 5, 9, and 12. A computer program was used to randomly assign the TPOAb(+) patients to either group S1 or group S0. A sealed opaque envelope was assigned to each patient; only the doctor who treated the patient, and who did not participate in any subsequent phase of the study, knew to which group the patient was assigned. Different medical doctors participated in different phases of the protocol, so that each was unaware of the group to which the patients belonged.

In group S1, six patients had spontaneous miscarriages, and two abandoned the study for personal reasons. Of the remaining 77 women, 67.5% underwent all eight planned thyroid tests, 72.7% underwent seven of eight, 83.1% underwent six of eight, and all 77 participants underwent at least five of eight thyroid tests. In group S0, seven patients had spontaneous miscarriages, and three abandoned the study for personal reasons. Of the remaining 74 women, 70.3% underwent all eight planned thyroid tests, 75.7% underwent seven of eight, 83.8% underwent six of eight, 91.9% underwent five of eight, and all 74 participants underwent at least four of eight thyroid tests. In group C, two patients had spontaneous miscarriages, and two abandoned the study for personal reasons. Of the remaining 81 women, 56.8% underwent all eight planned thyroid tests, 70.4% underwent seven of eight, 82.7% underwent six of eight, 93.8% underwent five of eight, and all 81 participants underwent at least four of eight thyroid tests.

Blood Se concentrations were measured at the first endocrinological visit (9.4 ± 2.7 wk gestation), at 20 and 30 wk gestation, at delivery, and at 6 and 12 months after delivery. In group S1, 68.8% took all six of the planned Se dosages, 71.4% took five of six, 83.1% took four of six, and all 77 participants took at least three of six Se dosages. In group S0, 71.6% took all six of the planned Se dosages, 90.5% took five of six, 85.9% took four of six, and all 74 participants took at least three of six Se dosages. In group C, 60.5% took all six of the planned Se dosages, 83.9% took five of six, 90.1% took four of six, and all 81 participants took at least three of six Se dosages.

Thyroid ultrasound (US) scans

An independent radiologist performed thyroid US scanning (high-resolution US, 7.5 MHz; Esaote, Italy) at the first endocrinological visit during pregnancy, at delivery, and at the end of the postpartum period. The echogenicity of the thyroid parenchyma was classified as normal (grade 0) or mild thyroiditis (grade 1), moderate thyroiditis (grade 2), or advanced thyroiditis (grade 3). For the purposes of this study, the presence of nodules or cysts was disregarded in classifying the background thyroid parenchyma. All the patients belonging to groups S1 and S0 underwent the three planned US scans; in group C, 91.3% underwent all three planned US scans, and all 81 patients underwent at least two of three US scans.

Assays

Serum TSH and F T_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. Intraassay and interassay coefficients of variation were 2.3% and 9.2% for TSH and 4.3% and 6.8%, respectively, 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. Serum Se levels were determined in duplicate using an atomic absorption spectrometer (Spectra 300; Varian, Australia). The detection limit for Se was 7.0 μg/liter; intraassay and interassay coefficients of variation coefficients of variation were 1.8% and 4.2%, respectively.

To avoid any fetal/obstetrical complications due to relatively reduced FT_4 values in TPOAb(+) women, levothyroxine (LT_4) treatment was initiated during pregnancy if patients had TSH values above the normal range and/or FT_4 values below the normal range. After delivery LT_4 administration was stopped, and substitutive treatment, in case of hypothyroidism, was initiated for participants with TSH values higher than 10 mIU/liter. Patients whose substitutive treatment was initiated during the postpartum period (within 12 months after delivery) stopped receiving LT_4 at the end of the postpartum period to determine whether the condition of hypothyroidism was permanent. During pregnancy LT_4 administration was titrated to keep FT_4 values in the middle-higher tertile and TSH less than 2.5 mIU/liter; after pregnancy LT_4 was titrated to keep TSH and FT_4 within the normal range.

Postpartum thyroid dysfunction (PPTD)

After delivery, patients were considered hypothyroid if their TSH values were above the normal range, whether or not their FT_4 values were below or in the normal range; they were considered hyperthyroid when their TSH values were below the normal range, whether or not their FT_4 values were above or in the normal range.

Statistical analysis

A statistical analysis was performed using an SPSS program (SPSS, Inc., Chicago, IL). Data were analyzed using an ANOVA test for multiple groups; the Duncan test was performed to compare the results from different groups at each time point of the study. All tests were considered statistically significant at $P < 0.05$. To avoid a type I statistical error, a power calculation was performed. Given that the placebo group (S0) displayed PPTD in 48.6% and permanent hypothyroidism in 20.3% of cases, and the treated group (S1) in 28.6 and 11.7%, respectively, the minimal number needed for $P < 0.05$ was 68 cases in each group.

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

Results

The age range was 18–36 yr, with a Gaussian distribution (mean ± SD and 28 ± 5), with no differences between groups. The first endocrinological visit occurred at gestational wk 9.4 ± 2.7, with no differences between groups. The time of Se/placebo initiation was 12.5 ± 0.9 wk, with no difference between group S1 and S0 (Table 1).

Maternal and neonatal complications

Besides the aforementioned miscarriages, the other obstetrical complications (hypertension, preeclampsia, placental abruption, and premature deliveries) and clinical char-

TABLE 1. Characteristics of patients

	Group S1 (n = 77)	Group S0 (n = 74)	Group C (n = 81)	*P* value
Age (yr)	28 ± 6	28 ± 5	27 ± 5	ns
Parity status (0/≥1)	60/17	56/18	59/22	ns
Baseline TSH (mIU/liter)	1.6 ± 0.6[a]	1.7 ± 0.7[a]	0.9 ± 0.4[b]	<0.01
Baseline FT_4 (ng/liter)	12.4 ± 2.2	12.2 ± 2.1	14 ± 2.1	ns
First endocrinological visit (wk)	9.6 ± 3.2	9.4 ± 2.5	9.5 ± 2.8	ns
Time of Se/placebo start (wk)	12.7 ± 0.9	12.6 ± 1.0	12.7 ± 1.1	ns
Patients requiring LT_4 during pregnancy (%)	19.4[a]	21.6[a]	2.5[b]	<0.01
Hypothyroid after delivery (%)	5.2	6.8		ns

ns, Not significant.
[a] Higher than [b].

acteristics of newborns (weight, height, cranial perimeter, and APGAR score) did not vary between groups.

Thyroid function

Thyroid function during pregnancy. At the first thyroid function tests, groups S1 and S0 had similar TSH values (1.6 ± 0.6 and 1.7 ± 0.7 mIU/liter, respectively), which were higher than those of group C (0.9 ± 0.4 mIU/liter; $P < 0.01$). During pregnancy, 19.4% of participants in group S1 and 21.6% in group S0 required LT_4 substitutive treatment for low FT_4 and/or high TSH values, whereas just 2.5% did in group S0 ($P < 0.01$). In groups S1 and S0, the LT_4 administered was 52.4 ± 16 μg/d, with no difference between the two groups. Of the patients who required LT_4, 64.5% started treatment at 20-wk and 35.5% at 30 wk gestation.

Thyroid function after delivery. Two months after delivery, and after having stopped LT_4 treatment, 5.2% of group S1 and 6.8% of group S0 patients were hypothyroid.

Thyroid function during postpartum period (within 12 months after delivery). In group S1, during the postpartum period, 22 of 77 patients (28.6%) had thyroid dysfunction develop; at the end of the postpartum period, 11.7% had become permanently hypothyroid (Fig. 1).

In group S0, 36 of 74 patients (48.6%) had thyroid dysfunction develop; at the end of the postpartum period, 20.3% had become permanently hypothyroid. Groups S1 and S0 together had a hypothyroid pattern develop in 58.6% of cases, a biphasic pattern develop in 34.5%, and a hyperthyroid pattern develop in 6.9%. Groups S1 and S0 had similar patterns of thyroid dysfunction.

In group C, 3 of 81 patients (3.7%) had thyroid dysfunction develop; one experienced transient thyrotoxicosis and then become euthyroid within the postpartum period, whereas the other two had a biphasic pattern.

The number of patients who had PPTD and permanent hypothyroidism develop was lower in group S1 compared with group S0 ($P < 0.01$ and $P < 0.01$, respectively).

Trends in TPOAb titers

Trends in TPOAb titers during pregnancy. Groups S1 and S0 had similar TPOAb titers at 10 wk gestation (627 ± 42 and 580 ± 39 kIU/liter) (Fig. 2). Compared with baseline, both groups displayed a significant reduction of TPOAb during gestation. TPOAb reduction was greater in group S1 (62.4%) than in group S0 (43.9%) ($P < 0.01$).

Trends in TPOAb titers during the postpartum period (within 12 months after delivery). Both groups S1 and S0 experienced a sharp increase of antibodies after parturition until 5 months after parturition. The peak of titers was attenuated in group S1 compared with group S0 (383.4 ± 148 *vs.* 745.5 ± 257 kIU/liter) ($P < 0.01$). During the postpartum period, lower TPOAb titers were observed in group S1 compared with group S0 (323.2 ± 44 *vs.* 621.1 ± 80 kIU/liter) ($P < 0.01$).

Thyroid US

Thyroid US at 10 wk gestation. In group S1, 15.6% of patients had normal echogenicity of the thyroid parenchyma (grade

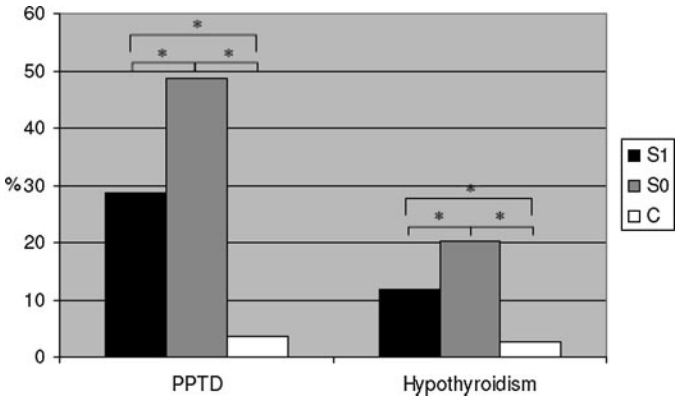

FIG. 1. Percentage of patients who had PPTD (*left*) and hypothyroidism (*right*) develop in TPOAb(+) women who received Se (group S1) or placebo (group S0), and in TPOAb(−) women (group C). *, $P < 0.01$.

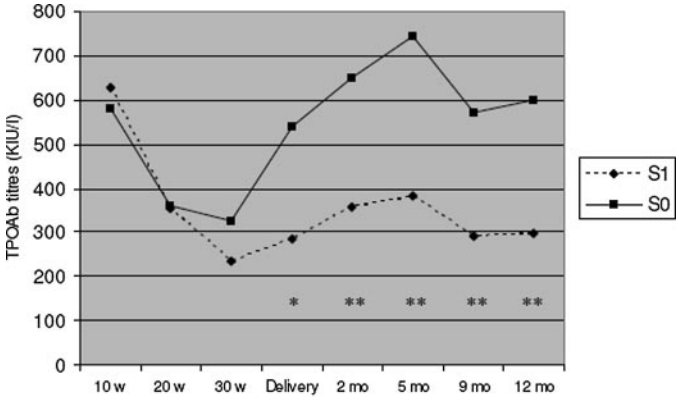

FIG. 2. Trends in TPOAb titers in TPOAb(+) women who received Se (group S1) or placebo (group S0). *, $P < 0.05$. **, $P < 0.01$. mo, Months; w, weeks.

0), whereas 59.7% had mild thyroiditis (grade 1), 15.6% moderate thyroiditis (grade 2), and 9.1% advanced thyroiditis (grade 3). In group S0, 13.5% of patients had normal echogenicity of the thyroid parenchyma (grade 0), whereas 63.5% had mild thyroiditis (grade 1), 21.6% moderate thyroiditis (grade 2), and 5.4% advanced thyroiditis (grade 3). Thus, 75.3% of patients in group S1 were grade 0–1, whereas 24.7% were grade 2–3; in group S0, 77% of patients were grade 0–1, whereas 23% were grade 2–3. The distributions of the grades of echogenicity pattern did not differ between groups S1 and S0.

Thyroid US at delivery. In group S1, 16.9% of patients had normal echogenicity of the thyroid parenchyma (grade 0), whereas 61% had mild thyroiditis (grade 1), 14.3% moderate thyroiditis (grade 2), and 7.8% advanced thyroiditis (grade 3). In group S0, 14.8% of patients had normal echogenicity of the thyroid parenchyma (grade 0), whereas 64.9% had mild thyroiditis (grade 1), 12.2% moderate thyroiditis (grade 2), and 8.1% advanced thyroiditis (grade 3). At delivery, 77.9% of patients in group S1 were grade 0–1, whereas 22.1% were grade 2–3. In group S0, 79.7% of patients were grade 0–1, whereas 20.3% were grade 2–3. The distributions of the grades of echogenicity pattern did not differ between groups S1 and S0.

Thyroid US at the end of the postpartum period. In group S1, 10.4% of patients had normal echogenicity of the thyroid parenchyma (grade 0), whereas 62.3% had mild thyroiditis (grade 1), 16.9% moderate thyroiditis (grade 2), and 10.4% advanced thyroiditis (grade 3). In group S0, 10.8% of patients had normal echogenicity of the thyroid parenchyma (grade 0), whereas 44.6% had mild thyroiditis (grade 1), 35.1% moderate thyroiditis (grade 2), and 9.5% advanced thyroiditis (grade 3). At the end of the postpartum period, 72.7% of patients belonging to group S1 were grade 0–1, whereas 27.3% were grade 2–3. In group S0, 55.4% were grade 0–1, and 44.6% were grade 2–3. At the end of the postpartum period, the US echogenicity patterns in group S1 did not differ from the ones at the beginning of pregnancy and at delivery, whereas in group S0, the patterns significantly worsened compared with the patterns at the beginning of pregnancy and at delivery ($P < 0.05$ and $P < 0.05$, respectively). Furthermore, when comparing the echogenicity patterns of groups S1 and S0, the Se-supplemented group displayed a significantly lower percentage of grade 2–3 thyroiditis at the end of the postpartum period ($P < 0.01$).

Se concentrations

Se concentrations were similar in groups S1, S0, and C at 10 wk gestation (80.9 ± 2.4, 78.2 ± 2.3, and 78.8 ± 2.5 μg/liter, respectively). Afterward, Se concentrations in group S1 were higher at each time point with respect to groups S0 and C ($P < 0.01$) (Fig. 3). In group S1, Se concentrations were higher after supplementation with respect to baseline for the entire study period ($P < 0.01$). In groups S0 and C, Se levels significantly decreased at 30 wk gestation with respect to values at 10 wk gestation ($P < 0.05$), and after delivery returned to values similar to baseline. Se concentrations did not differ between groups S0 and C. During the study period, no adverse effects due to excess Se intake were observed in the Se-treated group.

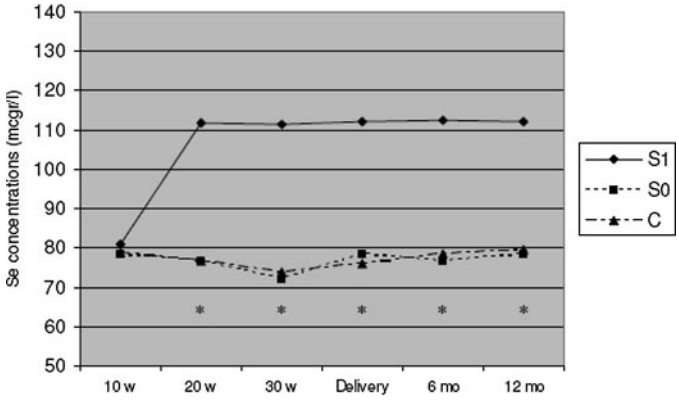

FIG. 3. Se concentrations during and after pregnancy in TPOAb(+) women who received Se (group S1) or placebo (group S0) and in TPOAb(−) women (group C). *, $P < 0.01$. mo, Months; w, weeks.

Discussion

Our study compared thyroid function, autoimmunity, and echogenicity patterns in TPOAb(+) women given Se supplementation or not during pregnancy and the postpartum period. PPT, whose prevalence ranges from 1.1–16.7%, with a mean prevalence rate of 7.2%, occurs much more frequently in women who are already TPOAb(+) during pregnancy (10). Lazarus *et al.* (11) showed that the highest risk of PPTD occurred in those women who had already suffered from a previous PPTD, with a 69% recurrence rate of the disease at subsequent pregnancy. PPTD in TPOAb(+) women varies widely, reaching values as high as 55% (12–16). The variability of PPTD in these patients may be due to the use of different screening procedures or different genetic and environmental risk factors. In particular, this lack of consensus may be explained by variability of the antibody dosages (microsomal or TPO), variations in assay methodology, and different times of screening during pregnancy and the postpartum period. Furthermore, the influence of disease definition, effects of variability of genetic predisposition, frequency of blood testing, and study design must be considered. However, all authors agree that the best predictors of the development of PPTD are age, TPOAb titers, TSH value, and US echogenicity (5, 16, 17). In our TPOAb(+) population study, Se supplementation significantly reduced the incidence of PPTD when compared with the untreated group. This shows that maximizing GPx activity may, at least in part, counterbalance the postpartum immunological rebound. The positive effects of Se supplementation during the postpartum period are revealed by the significantly lower TPOAb titers and better echogenicity pattern displayed by group S1 compared with group S0.

In the women we studied, Se supplementation strongly influenced TPOAb titers. In group S1 the reduction of titers, which is also induced by the state of partial immunosuppression occurring during pregnancy, was greater than in group S0, and lower titers were observed throughout the postpartum period. The US echogenicity pattern also differed between the two groups. At the end of the postpartum

period, most of patients in the Se-supplemented group showed normal or mild thyroiditis, whereas most of the patients in the placebo group showed moderate or advanced thyroiditis. The positive effects exerted by Se on chronic thyroid inflammatory processes have already been shown in several publications, even when supplementation has been applied for shorter time periods than in this study. Gärtner *et al*. (7) administered 200 μg/d sodium selenite to TPOAb(+) women (on substitutive treatment with LT_4) for 3 months, resulting in a significant reduction of TPOAb titers with no effect on TgAb. The changes in TPOAb titers were accompanied by an amelioration of US echogenicity, whereas no significant changes were observed in required LT_4 substitutive dosages. Duntas *et al*. (8) confirmed the findings of Gärtner and Gasnier (18), showing a 55% reduction in TPOAb titers in a 6-month follow-up study. Two additional points about Se administration must be noted. The first is that as Se is stopped, TPOAb titers increase again because its effect is not long lasting. The second is that TPOAb reduction is dose-dependent and requires doses higher than 100 μg/d to maximize GPx activity (8).

Conflicting data have been published about variations of plasma Se concentration during pregnancy. Plasma Se concentrations have been either similar or decreased during pregnancy with respect to those in nonpregnant women (19–22). In our population of pregnant women, Se concentrations at the first trimester were around the lower recommended limit and decreased significantly at the third trimester in both groups not given Se supplementation (groups S0 and C). This confirms that pregnant women in developed countries may also be at risk for Se deficiency (23). In addition to the antioxidant and detoxifying properties exerted by the selenoproteins thioredoxin reductases and GPx, the deiodinases D1, D2, and D3 have an important regulatory role in the activation and inactivation of the thyroid hormones in all tissues. In areas markedly deficient in Se and iodine, Se supplementation alters thyroid hormone concentrations in euthyroid subjects and induces a dramatic reduction in the already impaired thyroid function in hypothyroid subjects; in these populations Se supplementation is not recommended without adequate and simultaneous iodine supply (24–26). Very low or very high Se intake (47 and 297 μg/d, respectively) alters thyroid hormone concentrations by reducing T3 in case of low, and increasing T3 in case of high Se intake (27). In countries where plasma Se is adequate or close to adequate, Se supplementation does not significantly affect thyroid hormone concentrations; this lack of effect has also been shown in euthyroid women with subtle thyroid hormone synthesis defects (*i.e.* a positive iodine-perchlorate discharge test) (28–30). In our study population, comparing the Se-supplemented group with the placebo group, no significant differences in thyroid hormone concentrations were observed; the lack of significant differences was observed both between the whole groups and between subgroups of patients composed of women who did or did not require substitutive LT_4 treatment. This finding might be due to the fact that baseline Se concentrations were adequate or close to adequate, whereas deiodinase activity decreases only in severe Se deficiency (31). The Se deficiency in our patients was mild or absent, and this might explain why the Se exhibited antiinflammatory activity without affecting thyroid hormone levels. It is known that GPx activity is impaired in individuals with low-normal plasma Se concentrations because the mean concentration necessary for optimal GPx activities is around 1.14 μmol/liter (32). In pig thyroid epithelial cells, H_2O_2-induced apoptosis is caspase-dependent, and both programmed thyroid cell death and necrosis elicited by H_2O_2 are highly sensitive to reduced selenite and GPx levels, confirming that Se deficiency is potentially harmful to the thyroid (33).

Conclusions

We have shown for the first time that Se supplementation during and after pregnancy inhibits the progression of autoimmune chronic thyroiditis. Se administration in the dosage of 200 μg/d during pregnancy and the postpartum period exerted an antiinflammatory action, reduced TPOAb titers, and ameliorated the US echogenicity pattern with respect to controls. Se supplementation improved the course of the destructive thyroid gland process that occurs after parturition, reducing the incidence of PPTD and hypothyroidism. Determining whether these beneficial effects are reverted as Se supplementation is stopped or whether they may be maintained for a long time if Se is continued will require further investigation.

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