0021-972X/90/7102-0274$02.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 71, No. 2
Printed in U.S.A.

Editorial: Thyroid Status in Normal Pregnancy

Hormonal changes and metabolic demands during pregnancy result in complex alterations in the biochemical parameters of thyroid function. Many of the changes are due to an elevated T_4 binding globulin (TBG) concentration which is induced by increased estrogen production during pregnancy. These gestational changes in thyroid function have raised questions about the activity of the thyroid in pregnant women.

Before the introduction of chemical measures of thyroid function, the frequent presence of goiter and the elevated BMR in pregnant women suggested a hyperactive thyroid. This impression was reinforced by the histologic picture of follicular hypertrophy and hyperplasia found in the thyroids of pregnant women. More recently, the goiter has been attributed to the increased glomerular filtration rate in pregnancy which results in an increased renal loss of iodine. In iodine-deficient areas, the thyroid gland compensates by enlarging and increasing the plasma clearance of iodine to produce sufficient thyroid hormone to maintain the euthyroid state.

The decreased plasma inorganic iodine concentration during pregnancy results in a smaller iodine pool and an increased thyroid clearance of iodine. Since the thyroid radioiodine uptake depends on the size of the iodine pool in addition to thyroid-stimulating activity, the thyroid radioiodine uptake is elevated in pregnancy. Although contraindicated, when pregnant women have been studied, the radioactive iodine thyroid uptake has been increased.

Thyroid function was originally monitored by the BMR, which was elevated in pregnant women. The BMR began to increase during the fourth month of gestation and continued to rise slowly until the eighth month with an overall 15–20% increase under rigorous basal conditions. The fetoplacental unit accounted for 70–80% of the increased oxygen consumption. Increased maternal cardiac output accounted for the rest.

Explanation of these findings has led to general acceptance that the normal pregnant woman is, in fact, euthyroid and has been reinforced by the observation that net T_4 turnover and, presumably, thyroid hormone requirements were unchanged in normal human pregnancy. (1) Net T_4 turnover was 90 μg/day in nonpregnant women and 97 μg/day in pregnant women. The two values were identical when expressed as the daily turnover per square meter of body surface.

However, the presence of thyroid stimulatory activity in sera of normal pregnant women (2), elevated hCG concentrations during the first trimester and the lower TSH concentration often observed early in pregnancy do raise the possibility of some degree of thyroid hyperfunction in early pregnancy.

The issue of thyroid status during pregnancy is of more than academic interest. Hypothyroid animals have difficulty in maintaining their pregnancies. In a study of 244 pregnant hypothyroid women, the role of stillbirth was double that of controls (3). However, myxedematous women have been reported to carry their pregnancies to term successfully. Additionally, there is also the controversial question of maternal transfer of thyroid hormone to the fetus (4). Available evidence suggests that T_3 and T_4 cross the placenta but do so with difficulty. Placental transfer of thyroid hormone may vary with the stage of gestation and aging of the placenta.

In a recent study of patients with peroxidase deficiency, evidence was presented that thyroid hormone does cross the placenta although not in sufficient amounts to render the fetus euthyroid (5). In thyrotoxic women treated with antithyroid drugs, the maternal free T_4 at delivery was the best indicator of the neonatal T_4 concentration, again suggesting placental transfer. The suggestion has been made that maternal T_4 plays a vital role in early fetal neurogenesis (6). Animal studies have supported the importance of cerebral thyroid hormone concentrations during the critical period of brain development.

Although there are numerous studies which have determined thyroid function during pregnancy, the availability of more sensitive and specific tests have prompted a reevaluation by Glinoer and his colleagues (7) on a large sample of 606 women which is reported in this issue. The authors found that serum T_4 and T_3 concentrations did not increase as much during pregnancy as would be expected by the increase in TBG. In approximately one-third of the pregnant women, relative hypothyroxinemia was present with a higher serum TSH concentration relative to other women in the study. The T_3/T_4 ratio was increased, compatible with preferential

Received May 2, 1990.
Address requests for reprints to: Gerard N. Burrow, M.D., University of California, San Diego, School of Medicine, La Jolla, California, 92093-0602.

0021-972X/91/7302-0421$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 73, No. 2
Printed in U.S.A.

Pregnancy in Patients with Mild Thyroid Abnormalities: Maternal and Neonatal Repercussions*

DANIEL GLINOER, MARISA FERNANDEZ SOTO†, PIERRE BOURDOUX, BERNARD LEJEUNE, FRANÇOIS DELANGE, MARC LEMONE, JACQUES KINTHAERT, CLAUDE ROBIJN, JEAN-PAUL GRUN, AND PHILIPPE DE NAYER

Departments of Endocrinology (D.G.), Nuclear Medicine (D.G., P.B., J.K.), Gynecology and Obstetrics (B.L., C.R., J.P.G.), Pediatrics (F.D.), and Radiology (M.L.), Saint-Pierre Hospital, Université Libre de Bruxelles, Brussels; and the Department of Nuclear Medicine, Clinique Saint-Luc, Université Catholique de Louvain (P.D.N.), Woluwe, Belgium

ABSTRACT. A prospective study was undertaken during pregnancy in 120 euthyroid women presenting with mild thyroid abnormalities (TA): 11 with a past history of thyroid disorder, 44 with goiter, 20 with nodules, and 45 with thyroid autoantibodies. The aims of the study were to assess whether the pattern of thyroid alterations during gestation was different in women with TA compared to that in healthy control pregnant subjects and to evaluate possible obstetrical and neonatal repercussions.

The overall prevalence of underlying subtle thyroid abnormalities in the cohort was 17%, probably as the result of the environmental moderately low iodine intake. Despite the intrinsic heterogeneity of the four groups of women with TA, the adaptation of the thyroid to the stress of pregnancy was different from that of the control subjects. Noteworthy were 1) the marked elevation of serum thyroglobulin in women with past history of thyroid disorder, goiter and thyroid nodules; 2) the increase in goiter size in a third of the goitrous women, associated with biochemical evidence of functional stimulation of the gland; 3) the indirect evidence of partial thyroidal autonomy in goitrous patients; and 4) the increase in the number and size of thyroid nodules during gestation. Taken together, the data indicated that pregnancy was associated with a greater thyroidal risk in patients with TA compared to healthy subjects.

In relation to thyroid autoimmunity, most patients remained euthyroid during gestation, but in a few cases, TSH was elevated at delivery, suggesting diminished thyroidal reserve. Also, 40% of newborns from mothers with thyroid autoimmunity had elevated thyroid peroxidase antibody titers at birth, and there was a highly significant correlation between maternal and neonatal thyroid peroxidase antibody titers. Finally, thyroid autoimmunity was clearly associated with an increased risk of spontaneous abortion (13.3 *vs.* 3.3%; $P < 0.001$)

Thyroid function in newborns from mothers with TA was normal and not different from that in controls; similarly, obstetrical features were similar in patients with TA and control subjects.

In conclusion, pregnancy is associated with a greater thyroidal risk in women with TA, thereby emphasizing a potential link between pregnancy and thyroid disorders. It is recommended that patients with known, even subtle, thyroid abnormalities be closely monitored during pregnancy, in particular those with a goiter, nodules, or thyroid autoimmunity, especially in areas with a moderately low iodine intake, where the prevalence of mild thyroid disturbances is high. (*J Clin Endocrinol Metab* **73:** 421–427, 1991)

IN A RECENT report, we presented the results of a large prospective study of healthy women during pregnancy, which was undertaken to evaluate the changes in maternal thyroid economy occurring during gestation (1). The study was performed in an area with a moderately low iodine intake, representative of many Western European cities (2–4). The following main features were found. Maternal thyroidal activity adjusted to the marked increase in serum T_4-binding globulin (TBG), but there was an overall reduction in the T_4/TBG ratio associated with lower free T_4 and T_3 levels. In most cases, however, free hormone levels remained within the reference ranges of nonpregnant subjects. Moreover, the adjustment of thyroidal secretion of T_4 and T_3 did not occur equally in all subjects and led, in approximately one third of the subjects, to more pronounced alterations in thyroid function, including relative hypothyroxinemia, increased T_3/T_4 ratios (presumably indicating preferential T_3 secretion), and increased, although normal, serum TSH concentrations. Also, high hCG levels during the first trimester of gestation were associated with stimulation of the thyroid, most likely

Received October 18, 1990.
Address requests for reprints to: Dr. Daniel Glinoer, Laboratory of Radioisotopes, Hôpital Saint-Pierre, 322 rue Haute, B-1000 Brussels, Belgium.
* This work was supported by Henning (Berlin), Triosol (Brussels), and the Fonds National Belge de la Recherche Scientifique (Contract 3.4531.91 to D.G.).
† Present address: Department of Endocrinology, Hospital San Cecilio, University of Granada, Spain.

due to a direct TSH-like effect of hCG on the thyroid. In addition, a marked increase in serum thyroglobulin (TG) levels was observed, especially during the last trimester. Finally, increased thyroid volume was common, and goiter was found in 9% of the women at delivery (1).

The present study deals with a group of euthyroid women investigated from the same cohort, but who had not been included in the previous report because they presented detectable thyroid abnormalities at entry. The aim was to compare this group to the data gathered in the healthy subject in order to assess whether the pattern of thyroid alterations during pregnancy was different in women with thyroid abnormalities (TA). We also compared possible obstetrical repercussions as well as thyroid function at birth in newborns from patients with TA and healthy subjects.

Subjects and Methods

Subjects and design of study

The cohort encompassed a total of 726 pregnancies, investigated both cross-sectionally and longitudinally from initial presentation to delivery. During the initial evaluation, a detailed history of past gynecological events was obtained, and gestational age was determined by fetal echography using standard procedures. Mean gestational age at booking was below 20 weeks in more than 70% of the pregnancies. A detailed history of thyroid-related past events was recorded, and the thyroid was carefully palpated. The study protocol was accepted by the ethical committee of the Faculty of Medicine, and the subjects gave informed consent at the initial presentation.

Among the cohort, 603 healthy pregnant women had no detectable thyroid abnormality and constituted the control group. On the basis of the initial evaluation, 120 euthyroid women were selected because they had discrete thyroid abnormalities and constituted the study group. Three patients with overt thyroid dysfunction were excluded. Based on the information available after initial evaluation, patients with TA were classified into 4 groups: 1) past history (PH; n = 11), women without goiter, nodules, or thyroid autoantibodies who were aware of a past thyroid disorder (such as a goiter during adolescence or short term treatment with thyroid hormones); 2) goiter (G; n = 44), women with an enlarged thyroid volume confirmed by echography and without thyroid autoantibodies; 3) nodularity (N; n = 20), women with a normal thyroid volume (*i.e.* ≤22 mL) presenting small nodules, most often disclosed by echography alone, and without thyroid autoantibodies; and 4) autoimmune thyroid disorders (AI; n = 45), women with detectable thyroid autoantibodies regardless of echographic findings.

The following parameters were determined at initial presentation: total T_4 and T_3, free T_4, TBG, TG, TSH, iodine concentration in a random urine sample, thyroid autoantibodies, and thyroid volume (TV). In addition, a second blood and urine sample was obtained at 32 weeks gestation, and the same determinations were carried out (except for thyroid ultrasonography). Information relevant to fetal development was assessed by measuring human placental lactogen (hPL), total estradiol (E_2), and free estriol (E_3) levels in maternal serum during late gestation (32 weeks). The last series of determinations in mothers, including ultrasonography and parameters of thyroid function, were performed 3 days after delivery. Finally, thyroid function tests (total T_4 and T_3, free T_4, TSH, and TG) were performed on cord serum in all newborns, and thyroid autoantibodies were measured in selected cases.

Methods

Total T_4 and T_3, TBG, TG, total E_2, free E_3 (Medico-Service, Benelux), hPL, and hCG were measured by conventional RIAs. For the determination of serum TG in the presence of endogenous TG antibodies, the recovery of radiolabeled TG added to test serum was first assessed, and only those sera yielding greater than 80% recovery were considered valid and included in the calculations. Free T_4 was determined using the two-step Gamma-Coat [^{125}I]free T_4 (Clinical Assays, Baxter, Cambridge, MA). Serum TSH was determined using a sensitive immunoradiometric assay (RIAbead II, Abbott, Chicago, IL). Anti-TG autoantibodies were measured by a solid phase RIA (5). Thyroperoxidase autoantibodies (TPO-Ab) were determined using the DYNO-test anti-TPO kit, kindly provided by Henning Gmbh (Berlin, Germany) (6). Urinary iodine concentration was assessed using a fully automated Technicon Autoanalyzer, employing the Sandell-Kolthoff reaction (7). Conventional thyroid ultrasonography was carried out using a short focused, small parts 7.5-mHz transducer (SAL-77, Toshiba, Tokyo, Japan). The volume of each lobe was estimated using the geometric formula to calculate the volume of an ovoid: volume = $(\pi/6) \times W \times H \times T$ (where W, H, and T represent width, height, and thickness). Total TV corresponded to the sum of both lobes (1). Statistical analyses of the data were carried out using the SPSS program (Statistical Package for Social Sciences) (1, 8), employing parametric and nonparametric tests as appropriate, on a PC-compatible Elite-AT computer (Compuline, Brussels, Belgium).

Results

On the basis of the criteria defined, 120 women among 726 pregnancies were considered to have mild TA, yielding an overall prevalence of 17% in a population of childbearing age women enrolled in consecutive order, thereby minimizing bias in selection.

Maternal parameters and spontaneous abortion rates

Table 1 compares maternal parameters for age, gestity (*i.e.* the number of previous pregnancies), and parity in patients with TA and control subjects. In all groups with TA the mean age was higher, with an average difference of 2 yr [all women with TA, 29.3 *vs.* 27.3 for controls; $P < 0.001$, by analysis of variance (ANOVA)]. Consequently, gestity and parity were slightly greater in women

TABLE 1. Maternal clinical parameters and spontaneous abortion rate

	PH (n = 11)	G (n = 44)	N (n = 20)	AI (n = 45)	Controls (n = 603)
Age (yr)	30 ± 2	29 ± 1[a]	31 ± 1[c]	29 ± 1[b]	27 ± 1
Gestity	2.4 ± 0.4	3.6 ± 0.3[b]	3.7 ± 0.5[a]	2.8 ± 0.3	2.9 ± 0.1
Parity	1.0 ± 0.4	2.2 ± 0.3[b]	2.4 ± 0.5[b]	1.5 ± 0.3	1.5 ± 0.1
Spontaneous abortion rate (%)	8.0	2.3	5.0	13.3[d]	3.3

Results are expressed as the mean ± SEM for age, gestity, and parity and as percent occurrences for abortions.

[a] $P < 0.1$ *vs.* control (by one-way ANOVA).

[b] $P < 0.05$ *vs.* control (by one-way ANOVA).

[c] $P < 0.01$ *vs.* control (by one-way ANOVA).

[d] $P < 0.005$ *vs.* control (by χ^2 analysis).

with TA compared to controls [3.9 *vs.* 2.9 gestations (P = NS); 1.8 *vs.* 1.5 children ($P < 0.05$, by ANOVA)]. Among the four groups with TA, differences in gestity and parity were significant only for patients with goiter and nodularity.

Table 1 also shows the rates of spontaneous abortions during the course of the present study. While only 3.3% of controls suffered spontaneous abortion, the rate was significantly higher in women with TA (10 of 102; 8.3%; $P < 0.02$, by χ^2 analysis). Interestingly, the high rate of fetal loss was primarily due to abortions occurring in women with thyroid autoantibodies (6 of 45 *vs.* 20 of 603 in controls; $P < 0.005$, by χ^2 analysis). Furthermore, it was shown by age-matched analysis that the high rate of abortions in women with TA was independent of the small age difference compared to healthy women. Serum TSH levels were similar in aborters with autoimmune features compared to aborters among the control population. Finally, in multiparous women the cumulated rates of spontaneous abortions during previous pregnancies ranged from 13–23%, but were not different in patients with TA compared to control subjects.

Thyroid parameters at initial presentation

Figure 1 illustrates the results of thyroid function tests, TG levels, and TV in patients with TA and control subjects at booking. For patients with PH, serum TSH and TV were similar to control values, while the saturation of TBG and free T_4 levels were significantly higher. These differences could be accounted for in part by the lower gestational age at booking of PH patients compared to controls (11 *vs.* 15 weeks; $P < 0.03$). However, despite a lower gestational age and similar thyroid volume, mean serum TG values were significantly higher in PH patients than in controls (52 *vs.* 31 μg/L; $P < 0.05$).

Patients with G, by definition, had an increased TV, ranging between 22–58 mL, with a mean of 29 mL, *i.e.* 2.4-fold TV of controls. As expected, these patients exhibited significantly higher TG levels than controls. They also had significantly higher TBG saturation and free T_4 levels in spite of identical gestational ages. Con-

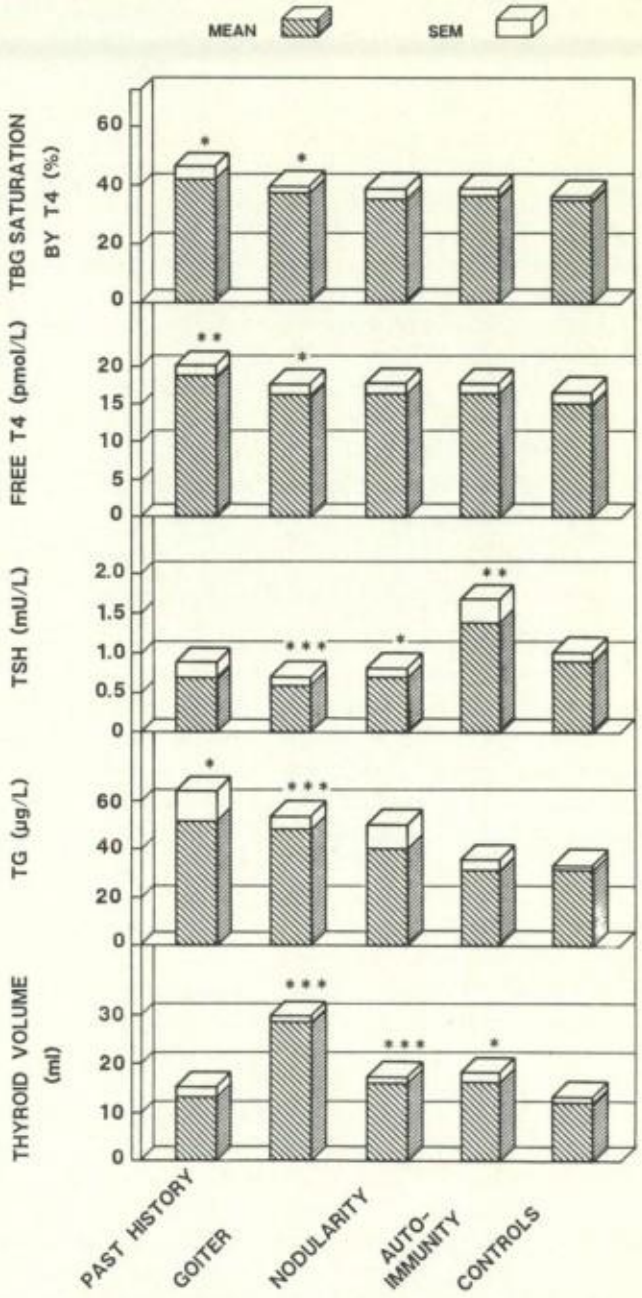

FIG. 1. Mean (±SE) results for the TBG saturation levels; free T_4, TSH, and TG concentrations; and TV in patients with TA and healthy controls at initial presentation. Statistical analysis was carried out by one-way ANOVA (patients *vs.* controls): *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$. The level of TBG saturation by T_4 corresponds to the molar T_4 to TBG ratio, expressed as a percentage, and was calculated for each individual data set. Reference ranges for nonpregnant female subjects are 28–60% for TBG saturation, 10–26 pmol/L for free T_4, 0.3–4.5 mU/L for TSH, 0–30 μg/L for TG, and 22 mL or less for TV. For TG and TSH, all statistical analyses were carried out after log transformation of the data.

versely, patients with G had a lower mean serum TSH (0.6 mU/L) than controls (0.9 mU/L; $P < 0.001$), even though the mean hCG levels were not different in the two groups (27,000 *vs.* 25,000 IU/L).

In patients with N, the mean TBG saturation levels and free T_4 and TG concentrations were similar to control values. There was a slight but significant increase in mean TV (16 *vs.* 12 mL; $P < 0.001$) and a decrease in mean basal TSH (0.7 *vs.* 0.9 mU/L; $P < 0.05$), as was the case for patients with G.

Finally, in patients with AI, there was a slight but significant increase in mean TV compared to the control values (16 *vs.* 12 mL; $P < 0.02$). In addition and in contrast to the two previous groups of patients, mean serum TSH was significantly higher (1.4 *vs.* 0.9 mU/L; $P < 0.01$), while the other parameters of thyroid function were not different from those in controls.

Changes in thyroid parameters during gestation

As reported in our original study (1), gestation in healthy subjects was associated with a decrease in both the saturation level of TBG and free T_4 concentrations. The changes occurred progressively with increasing gestational age, and a plateau was maintained during the last months. In patients with TA, the overall decrements in the level of TBG saturation (25%) and free T_4 concentration (17%) were significantly more pronounced than those in control subjects (17% *vs.* 8%; $P < 0.01$). In control subjects, there was a slight increase in TSH levels, mainly during the latter part of pregnancy, but the changes took place within the reference limits of nonpregnant female subjects. Among patients with TA, the overall increment in TSH was variable and not statistically different from that in control subjects (119% *vs.* 118%). However and in contrast to controls, 6% of patients with TA had, at delivery, abnormally high serum TSH levels (from 5–10 mU/L). Gestation was also associated with a marked increase in TG levels, as observed during the first months of gestation in control subjects, with a further increase near term; 59% of subjects exhibited elevated serum TG concentrations (>30 μg/L) at delivery. Among patients with TA, an increase in TG above 30 μg/L was found in as many as 83% of patients with G, N, and PH at delivery. Finally, urinary iodine concentrations were identical in patients with TA and control subjects at initial presentation (median, 52 μg/L). During late gestation, a similar decrease in urinary iodine levels was observed in both groups (median at 32 weeks, 42 μg/L).

Specific characteristics in women with TA

In relation to echographic changes during gestation, two interesting findings were observed. In patients with N, comparison between echographies at initial presentation and delivery indicated that even though total TV did not increase significantly in these women, the number and size of nodules initially present were increased. In 60% of cases nodules showed a doubling in size; most of them corresponded echographically to microcysts, between 5–12 mm of diameter, and were, hence, clinically not palpated. Furthermore, in 4 of 20 cases new nodules, not present at initial presentation, were found at delivery.

In patients with G, a marked increase in thyroid size was observed in approximately one third of the cases, with an average increment of 32% (ranging from 17–55%). These subjects were characterized by a more pronounced relative hypothyroxinemia during gestation, with mean free hormone levels near the lower limit (12 ± 1 pmol/L), lower mean saturation of TBG (26 ± 4%), higher mean T_3/T_4 ratio (30 ± 5), as well as slightly but not significantly higher mean TSH (2.5 mU/L) than the remainder of patients with G, suggesting a higher degree of glandular stimulation.

Among patients with AI, 37 of 45 (82%) had elevated titers of TPO-Ab at initial presentation, in the other 8 patients only TG-Ab was found. In the patients with elevated TPO-Ab, the distribution of TPO-Ab titers showed a wide scatter and was asymmetrical, ranging between 101–10,000 U/mL. The median value was 380 U/mL, and in 25% of cases, TPO-Ab was greater than 1,000 U/mL. During gestation, a clear-cut drop in TPO-Ab titers was observed, averaging 70% of the initial values ($P < 0.001$, by Wilcoxon test). Hence, in 50% of women with initially elevated TPO-Ab, the titers reverted to normal at delivery, and TPO-Ab titers exceeding 1,000 U/mL were found in only 10% of cases. TPO-Ab titers were also determined on cord serum in 16 neonates born to mothers with elevated TPO-Ab at initial presentation. In 40%, TPO-Ab levels were elevated at birth, with titers ranging from 105–9,500 U/mL (median value, 403 U/mL). There was a highly significant positive correlation ($r = 0.961$; $P < 0.001$) between TPO-Ab titers in mothers 3 days after delivery and levels in their neonates (Fig. 2). All neonates had a serum TSH level on the fifth day of life below 20 mU/L, which is considered normal for age.

Fetal development parameters during gestation

Five clinical and biochemical parameters relating to fetal development during gestation are illustrated in Table 2 for patients with TA and control subjects. Gestational age and neonatal weight at birth were not significantly different between patients and controls, except in the group of patients with PH, in whom neonatal weight was slightly lower (at the limit of significance). Similarly,

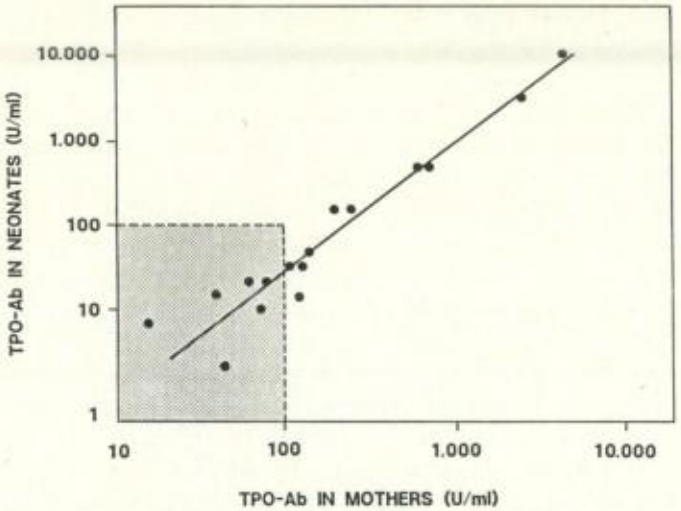

FIG. 2. TPO-Ab titers in mothers at delivery and neonates at birth in 16 paired data selected from mothers with abnormal TPO-Ab titers at initial presentation. The upper limit of the reference range is indicated by the *shaded area*.

TABLE 2. Obstetrical and fetal development indices

	PH (n = 11)	G (n = 44)	N (n = 20)	AI (n = 45)	Controls (n = 603)
Gestational age (weeks)	38 ± 2	39 ± 1	39 ± 1	39 ± 1	39 ± 1
Birth (kg)	2.9 ± 0.3[a]	3.3 ± 0.1	3.4 ± 0.1	3.3 ± 0.1	3.3 ± 0.1
hPL (mg/L)	6.9 ± 0.3[b]	6.0 ± 0.3	5.6 ± 0.7	5.7 ± 0.4	6.4 ± 0.1
Free E_3 (nmol/L)	29 ± 2[b]	29 ± 3	26 ± 4	32 ± 4	29 ± 1
Total E_2 (nmol/L)	77 ± 7[b]	85 ± 12	57 ± 13	90 ± 11	74 ± 2

Results are expressed as the mean ± SEM.
[a] $P < 0.1$ *vs.* control (by one-way ANOVA).
[b] hPL, free E_3, and E_2 were measured during late gestation (32 weeks).

serum levels of hPL, free E_3, and total E_2, determined at 32 week of gestation, indicated no significant difference among patients with TA or between patients and control subjects.

Neonatal thyroid function parameters

Thyroid function tests at birth are compared in Table 3 for the neonates born to mothers with TA and controls. All neonates exhibited low T_3/T_4 ratios (related to the classical low T_3 syndrome characteristic of thyroid function at birth), and there were no significant differences among the groups. Similarly, serum TSH and free T_4 concentrations were equivalent in all groups, except in babies born to mothers with PH, in whom TSH was unexpectedly lower. Finally, the highest mean levels of serum TG were found in neonates born to mothers with G and the lowest in those born to mothers with AI.

TABLE 3. Thyroid function in newborns

	PH (n = 11)	G (n = 44)	N (n = 20)	AI (n = 45)	Controls (n = 603)
T_3T_4 ($\times 10^3$)	5.4 ± 0.9	6.5 ± 0.4	5.5 ± 0.5	5.7 ± 0.4	6.0 ± 0.1
TSH (mU/L)	4.6 ± 0.7[c]	8.1 ± 1.0	8.4 ± 1.6	8.8 ± 1.3	7.6 ± 0.2
Free T_4 (pmol/L)	17 ± 1	20 ± 1	18 ± 1	20 ± 1	20 ± 1
TG (μg/L)	62 ± 1	84 ± 8[a]	75 ± 7	54 ± 6[b]	71 ± 2

Results are expressed as the mean ± SEM.
[a] $P < 0.1$ *vs.* control (by one-way ANOVA).
[b] $P < 0.05$ *vs.* control (by one-way ANOVA).
[c] $P < 0.01$ *vs.* control (by one-way ANOVA).

Discussion

The aims of the present study were to describe the alterations in thyroid function observed during gestation in euthyroid women with mild TA and to compare them with a cohort of healthy pregnant subjects. The authors are well aware that women with TA constitute a heterogenous group with distinct clinical entities. Nonetheless, they do represent together the most frequent underlying thyroid disorders in an unselected population of young women. Women with TA represented 17% of the entire cohort, a relatively high prevalence compared to data from the literature (9). The high prevalence is presumably due to three factors: 1) the thyroid abnormalities considered were mild, subclinical, and only detected in the majority of cases because of the sensitive methods employed; 2) the use of a highly sensitive technique to detect TPO-Ab increased the detection rate, compared, for instance, to microsomal antibodies (6); and 3) the study was performed in an area where the iodine supply in the population is borderline, well below WHO recommendations for pregnancy and the average intake in the U.S. (3, 4, 10). In epidemiological terms, the population under study was representative of the population in the center of Brussels, with approximately 40% being first or second generation immigrants, mainly of Mediterranean origin.

The main finding of the present study was that women with TA showed definite differences compared to control subjects, and several clinically relevant observations deserve comment.

Patients with PH had one interesting feature. Even though they had normal thyroid function tests, pronounced elevations in serum TG levels, both at initial presentation and throughout gestation, were present. At delivery, serum TG was abnormal in all individuals with PH and even higher than in other patients with TA. The results may indicate the high glandular sensitivity to the stimulatory processes affecting the thyroid during pregnancy in patients with PH.

Patients with G showed three distinct features. First, serum TG was significantly increased at the initial pres-

entation, a classical finding in goitrous patients (11, 12). Serum TG increased further near term, but the relative increment was not different from that in controls. Second, goitrous patients initially had a higher level of TBG saturation as well as free hormone concentrations, and conversely, TSH levels were lower compared to control values. Since glandular stimulation during early gestation depends in part on hCG levels (1, 13, 14), it was of interest that serum hCG was not higher in goitrous patients. Hence, for equivalent TSH-like activity of trophoblastic origin, goitrous patients presented with a more sustained thyroidal stimulation, at least during early gestation, perhaps related to underlying glandular autonomy. Third, the overall changes in TV were highly variable. Some goitrous patients showed no increase in TV, while in approximately one third of the cases, the increase in TV during gestation was significant. In those cases, the increment in TV was associated with a more pronounced stimulation of the thyroid.

In patients with N but without overall enlargement of the thyroid, the most significant finding was an increase in both the number and size of the nodules in a large number of women, a further suggestion of glandular stimulation during gestation.

In patients with AI, three findings should be emphasized. First, TPO-Ab titers decreased by more than 50% during gestation, and normalization of TPO-Ab was observed in half of the patients at delivery. Since these patients have a higher risk of developing postpartum thyroiditis, the present results indicate the usefulness of screening during early gestation and not, as suggested by some researchers, at the time of delivery (15). Second, most patients with AI remained euthyroid during gestation, but in a few cases TSH was elevated at delivery, suggesting diminished thyroidal reserve. Finally, 40% of neonates born to mothers with elevated TPO-Ab titers had elevated TPO-Ab at birth. The data indicated that the abnormality could be predicted in newborns in view of the high correlation with maternal TPO-Ab titers. All newborns were euthyroid at birth and had normal TSH levels on the fifth day of life (screening for congenital hypothyroidism), but the potential importance of the presence of elevated TPO-Ab titers, passively transmitted from the mother, remains to be further clarified.

Another important question concerns the rate of spontaneous abortions in women with AI. The present study indicates that, independent of age, women with thyroid auto-Ab clearly have an increased rate of abortion, although they are clinically and biochemically euthyroid. Similar findings were recently reported by Stagnaro-Green *et al.* (16), and the most plausible hypothesis is that such women present an underlying more generalized defect in autoimmunity, leading to increased fetal loss. Therefore, the early determination of thyroid auto-Ab, and in particular TPO-Ab, could serve as a sensitive marker to identify women at risk (6).

We also analyzed the possible repercussions on the child of the changes in thyroid parameters observed in the mother. Thyroid function tests were not different in neonates born to mothers with TA compared to controls. Similarly, obstetrical features, such as duration of gestation, weight of newborns at birth, APGAR indices, and maternal hormone determinations indirectly related to fetal development (hPL, E_2, and free E_3), were similar in patients with TA and controls.

The study was conducted in an area with a moderately low iodine intake, representative of many Western European cities (2–4). Our original hypothesis was that a marginally low iodine supply would lead to a further decrease in the availability of iodide for the maternal thyroid during pregnancy due to increased renal clearance (17) and losses to the feto-placental complex during late gestation (18), eventually resulting in relative iodine deficiency (19, 20). We also hypothesized in our original report that the thyroid stress due to pregnancy could eventually lead to thyroid pathology in predisposed subjects if the alterations were not entirely reversible after delivery (1). It is, therefore, noteworthy that the group of women with TA were 2 yr older and had had more numerous previous pregnancies than the controls. Even though not conclusive, the information provides a possible link between previous pregnancy and the later occurrence of thyroid disorders.

In conclusion, despite the intrinsic differences among women with TA, the adaptation of the thyroid to the stress of pregnancy occurred differently from that in control subjects. Taken together, the data indicate that pregnancy is associated with a greater thyroid risk in women with TA, thereby emphasizing the potential relation between pregnancy and thyroid disorders. It is recommended that patients with known, even subtle, thyroid abnormalities be closely monitored during pregnancy, in particular those with a G, N, or AI, especially in areas with a moderately low iodine intake, where the prevalence of mild thyroid disturbances is high.

Acknowledgments

The authors express their gratitude to all colleagues who have manifested interest and have been of considerable help in the realization of the study, in particular to Drs. C. Beckers, G. Copinschi, A. M. Ermans, H. Ham, H. Kleiner, G. Servais, and P. Wilkin. The authors wish to acknowledge the invaluable help of the nursing staff of the Department of Gynecology and Obstetrics and the Blood Sampling Center of Hospital Saint-Pierre, the technicians of the laboratories of Nuclear Medicine and Gynecology, particularly Mr. D. Connart, and the secretarial staff of the Out-Patient Clinic of Gynecology. The authors greatly acknowledge the secretarial expertise of Mrs. C. Guerit in the preparation of the manuscript, and thank Mr. Michel Candeur (Ecole de Santé Publique, Université Libre de Bruxelles) for his expert

assistance in the organization of the computer programs for data collection.

References

1. Glinoer D, De Nayer P, Bourdoux P et al. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab. 1990;71:276–87.
2. Gutekunst R, Scriba PC. Goiter and iodine deficiency in Europe. The European Thyroid Association report as updated in 1988. J Endocrinol Invest. 1989;12:209–20.
3. Delange F, Bürgi H. Iodine deficiency disorders in Europe. Bull WHO. 1989;67:317–25.
4. Bourdoux P. Borderline iodine deficiency in Belgium. J Endocrinol Invest. 1990;13:77.
5. Roman SH, Korn F, Davies TF. Enzyme-linked immunosorbent microassay and hemagglutination compared for detection of thyroglobulin and thyroid microsomal autoantibodies. Clin Chem. 1984;30:246–51.
6. Glinoer D, de Nayer P, Lejeune B, et al. Antithyroid peroxidase antibodies in normal pregnancy. In: Carayon P, Ruf J, eds. Thyroperoxidase and thyroid autoimmunity. Colloque INSERM/Libbey Eurotext; 1990;207:303–11.
7. Bourdoux P. Measurement of iodine in the assessment of iodine deficiency. IDD Newslett. 1988;4:8–12.
8. Nie NH, Hull CM, Jenkins JG, Steinbrenner K, Benta DM. Statistical package of the social sciences, 2nd ed., New York: McGraw Hill; 1975.
9. Tunbridge WMG. The epidemiology of thyroid diseases. In: Ingbar SH, Braverman LE, eds. The thyroid. A fundamental and clinical text, 5th ed., Philadelphia: Lippincott; 1986;625–33.
10. Braverman LE. Iodine-induced thyroid disease. In: Ingbar SH, Braverman LE, eds. The thyroid. A fundamental and clinical text, 5th ed., Philadelphia: Lippincott; 1986;735–46.
11. Pezzino V, Vigneri R, Squatrito S, Filetti S, Camus M, Polosa P. Increased serum thyroglobulin levels in patients with nontoxic goiter. J Clin Endocrinol Metab. 1978;46:653–7.
12. Refetoff S, Lever EG. The value of serum thyroglobulin measurement in clinical practice. JAMA. 1983;250:2352–7.
13. Kimura M, Amino N, Tamaki H, Mitsuda N, Miyai K, Tanizawa O. Physiologic thyroid activation in normal early pregnancy is induced by circulating hCG. Obstet Gynecol. 1990;75:775–8.
14. Yoshikawa N, Nishikawa M, Horimoto M, et al. Thyroid-stimulating activity in sera of normal pregnant women. J Clin Endocrinol Metab. 1989;69:891–5.
15. Nikolai TF, Turney SL, Roberts RC. Postpartum lymphocytic thyroiditis. Prevalence, clinical course, and long-term follow-up. Arch Intern Med. 1987;147:221–4.
16. Stagnaro-Green A, Roman SH, Cobin R, El-Harazy E, Alvarez-Marfany M, Davies TF. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. JAMA. 1990;264:1422–5.
17. Aboul-Khair SA, Crooks J, Turnbull AC, Hytten FE. The physiological changes in thyroid function during pregnancy. Clin Sci. 1964;27:195–207.
18. Fisher DA. Maternal-fetal thyroid function in pregnancy. Clin Perinatol. 1983;10:615–26.
19. Pochin EE. The iodine uptake of the human thyroid throughout the menstrual cycle and in pregnancy. Clin Sci. 1952;11:441–5.
20. Halnan KE. The radioiodine uptake of the human thyroid in pregnancy. Clin Sci. 1958;17:281–90.