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A Randomized Trial for the Treatment of Mild Iodine Deficiency during Pregnancy: Maternal and Neonatal Effects*

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ABSTRACT

One hundred and eighty euthyroid pregnant women were selected at the end of the first trimester of gestation on the basis of biochemical criteria of excessive thyroid stimulation, defined as supranormal serum thyroglobulin (TG >20 μg/L) associated with a low normal free T_4 index (<1.23) and/or an increased T_3/T_4 ratio (>25×10^{-3}). Women were randomized in a double blind protocol into three groups and treated until term with a placebo, 100 μg potassium iodide (KI)/day, or 100 μg iodide plus 100 μg L-T_4/day. Parameters of thyroid function, urinary iodine excretion, and thyroid volume were monitored sequentially. Neonatal thyroid parameters, including thyroid volume by echography, were also assessed in the newborns from mothers of the three groups.

In women receiving a placebo, the indices of excessive thyroid stimulation worsened as gestation progressed, with low free T_4 levels, markedly increased serum TG and T_3/T_4 ratio. Serum TSH doubled, on the average, and was supranormal in 20% of the cases at term. Urinary iodine excretion levels were low, around 30 μg/L at term. The thyroid volume increased, on the average, by 30%, and 16% of the women developed a goiter, confirming the goitrogenic stimulus associated with pregnancy. Moreover, the newborns of these mothers had significantly larger thyroid volumes at birth as well as elevated serum TG levels.

In both groups of women receiving an active treatment, the alterations in thyroid function associated with pregnancy were markedly improved. The increase in serum TSH was almost suppressed, serum TG decreased significantly, and changes in thyroid volume were minimized (group receiving KI) or almost suppressed (group receiving KI combined with L-T_4). Moreover, in the newborns of the mothers in the two groups receiving an active treatment, serum TG was significantly lower, and thyroid volume at birth was normal. The effects of therapy were clearly more rapid and more marked in the group receiving a combination of T_4 and KI than in the women receiving KI alone. The differences could be partly attributed to the slightly higher amount of iodine received by women in the combined treatment. However, the main benefits of the combined treatment were almost certainly attributable to the hormonal effects of the addition of L-T_4. Furthermore, the study demonstrated that the administration of T_4 did not hamper the beneficial effect of iodine supplementation.

In conclusion, the present work emphasizes the potential risk of goitrogenic stimulation in both mother and newborn in the presence of mild iodine deficiency. Furthermore, the results clearly indicate the benefits of supplementing pregnant women with iodine and women with excessive thyroid stimulation (or a preexisting goiter) with a combination of iodine and L-T_4. In conditions of mild iodine deficiency, pregnancy justifies monitoring thyroid function and volume, and therapeutic intervention to avoid hypothyroxinemia and goitrogenesis in both mother and newborn. (*J Clin Endocrinol Metab* **80:** 258–269, 1995)

FOR A FEW years, there has been renewed interest in the regulation of thyroid function during pregnancy. Our group has been involved recently in the investigation of several aspects of this question, dealing with the adjustment of maternal thyroid function in both healthy subjects (1) and women with mild underlying thyroid abnormalities (2), such as asymptomatic autoimmune thyroiditis (3), the goitrogenic stimulus of pregnancy in relation to iodine restriction (4, 5), and the repercussions in newborns of mothers with moderate iodine deficiency (6).

Pregnancy is accompanied by profound changes in thyroid economy (7–9). The challenge for the thyroid gland during pregnancy can be viewed as a mathematical fraction, with hormone requirements in the numerator and the availability of iodine for both the maternal and fetal thyroid glands in the denominator; the thyroid challenge arises because hormone requirements are increased during gestation, whereas the availability of iodine is reduced (10, 11).

In areas with a sufficient iodine intake (*i.e.* >150–200 μg/day) in the "natural" environment of the population, the thyroid machinery adjusts easily to maintain stable free

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hormone levels. There is good indication that in such conditions goitrogenesis does not occur frequently during pregnancy; changes in thyroid volume (TV) are minor and presumably related only to intumescence of the gland (12, 13). In areas with severe iodine deficiency (*i.e.* <50 μg intake/day), goitrogenesis as well as hypothyroidism are frequently observed in mother and newborn as a result of the inability of the thyroid gland to adjust to changes in thyroid economy associated with pregnancy (14, 15). Hence, the pregnant woman and the newborn have been considered primary targets for iodine supplementation in such areas (16, 17).

The iodine intake in the general population in the Brussels area is on the order of 50–80 μg/day, typical of most Western European countries, where no systematic addition of iodine to the diet is organized by governments (18–20). In such conditions, the iodine intake is probably sufficient for the daily needs of healthy adults as long as no other factor intervenes to disrupt the fragile balance between thyroid hormone requirements and iodine availability. It has been reported in our former studies that pregnancy acts to unmask the iodine deficiency; mild iodine deficiency is associated with excessive thyroid stimulation in a significant fraction of otherwise healthy pregnant women (1). One third of pregnant women have relative hypothyroxinemia, preferential T_3 secretion, elevated serum thyroglobulin (TG), and a negative iodine balance. The condition leads to goitrogenesis and the aggravation of preexisting goiter. Moreover, pregnancy constitutes a stimulus not only for the maternal thyroid, but also for the fetal thyroid gland; iodine deficiency is the key to explaining the high recall rates in screening programs for congenital hypothyroidism frequently reported in Europe (21).

On the basis of this background, we undertook a prospective trial to investigate the effects of treatment in women with excessive thyroid stimulation on thyroid function and goitrogenesis in both pregnant women and their offspring at birth. One hundred and eighty pregnant women, of a total of 2000 women who presented consecutively at the prenatal clinic, were selected on the basis of biochemical criteria of excessive thyroid stimulation described in *Materials and Methods*. They represented the extreme end of the distribution curve of thyroid status in healthy euthyroid pregnancies. The women were randomized in a double blind protocol into three groups (no active treatment, iodine supplementation alone, iodine combined with L-T_4). Thyroid function and volume were monitored until parturition. Neonatal parameters were also assessed in the babies born to the mothers of the three groups. Thyroid function in cord blood and TV were determined in the neonates in the first days of life.

Subjects and Methods

Patients enrollment and selection procedure

All consecutive pregnant women who attended the prenatal clinic in our institution for the first visit and had no history of thyroid disease were submitted to a systematic screening of thyroid function (serum total T_4 and T_3, T_4-binding globulin (TBG), TSH, and TG) and thyroid autoantibodies (thyroid peroxidase and TG). The protocol was approved by the ethical committee of the Faculty of Medicine. A total of 2000 women were screened between June 1990 and December 1992. On the basis of the initial tests, women with an abnormal serum TSH level (<0.2 or >4.0 mU/L) and/or positive antibodies were excluded from the present procedure.

Among the euthyroid pregnancies without antibodies, 3 criteria were defined on the basis of our previous work conducted in 606 consecutive healthy pregnancies (1) to characterize women with excessive thyroid stimulation: 1) an elevated serum TG level (>20 μg/L); 2) a low normal free T_4 index (≤1.23), as calculated from the T_4/TBG ratio (22); and 3) an elevated molar ratio T_3/T_4 ($\geq 25 \times 10^{-3}$). Patients were enrolled in the study if they were less than 16 weeks gestation and fulfilled criterion 1 associated with criteria 2 and/or 3. Figure 1 shows the distribution frequency of each criteria as it was applied by computer simulation to the cohort of 606 normal pregnancies reported previously (1). Each criteria corresponds approximately to the extreme tertile of the population. Combined as indicated above, the 3 criteria allowed together for the selection of 180 of 2000 women (9%), corresponding to women with a euthyroid status and presenting biochemical features of excessive thyroid stimulation.

Design of the study

Once selected, the women were met by 2 of the investigators. The general purpose of the study and its design were explained; women were requested to give a formal consent to enter the protocol. At this stage, the following tests were carried out: total T_4 and T_3, TBG, free T_4, TG, TSH, urinary iodine concentration, and TV determination by ultrasonography. The study was designed as a prospective double blind randomized trial, and the 180 women were subdivided into 3 equal groups. The first group (A) received a daily placebo; the second group (B) received 131 μg potassium iodide (KI)/day, corresponding to 100 μg iodide/day; the third group (C) received a combination of 131 μg KI and 100 μg L-T_4/day. Treatment was given from the day of enrollment until delivery. Serum and urine determinations were repeated in the second and third trimesters. After delivery (2–6 days), the same tests and the second ultrasonography were repeated in the mothers. Thyroid function parameters were determined in the neonates on cord blood, and thyroid echography was performed at the age of 3–6 days. Whenever possible, iodine in breast milk was also determined.

In terms of timing, the initial visit of pregnant women corresponded to 10.7 ± 0.3 (mean ± SEM) weeks gestation, booking to 14.4 ± 0.2 weeks, second trimester samples to 23.5 ± 0.2 weeks, third trimester samples to 31.9 ± 0.2 weeks, and delivery samples to 40 ± 0.1 weeks gestation.

Methods

Total T_4 and T_3, TBG, and TG were measured by conventional RIAs. The free T_4 index used in the screening was calculated from the ratio of total T_4/TBG (22). Free T_4 was determined using the two-step Gamma-Coat [^{125}I]free T_4 assay (Clinical Assays, Baxter, Cambridge, MA). Serum TSH was determined using a second generation immunoradiometric assay (RIAbead II, Abbott, North Chicago, IL); the reference range for TSH was 0.2–4.0 mU/L, determined from several thousand subjects from our Department of Endocrinology. In the screening tests, thyroid peroxidase antibodies were determined using the DYNO-test anti-TPO kit (Henning, Berlin, Germany), and thyroglobulin antibodies were determined by a sensitive RIA developed in our institution. Urinary and breast milk iodine concentrations were determined using a fully automated Technicon Autoanalyzer (Technicon, Tarrytown, NY), employing the Sandell-Kolthoff reaction (23). Thyroid ultrasonography was carried out in mothers, as previously described (1); normal TV ranged from 8–23 mL. In the newborns, thyroid ultrasonography was performed according to the procedure reported by Chanoine *et al.* (24). The distribution of normal TV in newborns ranged from 0.4–1.3 mL (10th and 90th percentiles), with a median value of 0.8 mL; values for neonatal TV above 1.5 mL were considered indicative of glandular hyperplasia.

Statistical analyses of the data were carried out using the SPSS program (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL) (25), employing parametric and nonparametric tests as appropriate, on a PC-compatible Elite AT computer (Compuline, Brussels, Belgium).

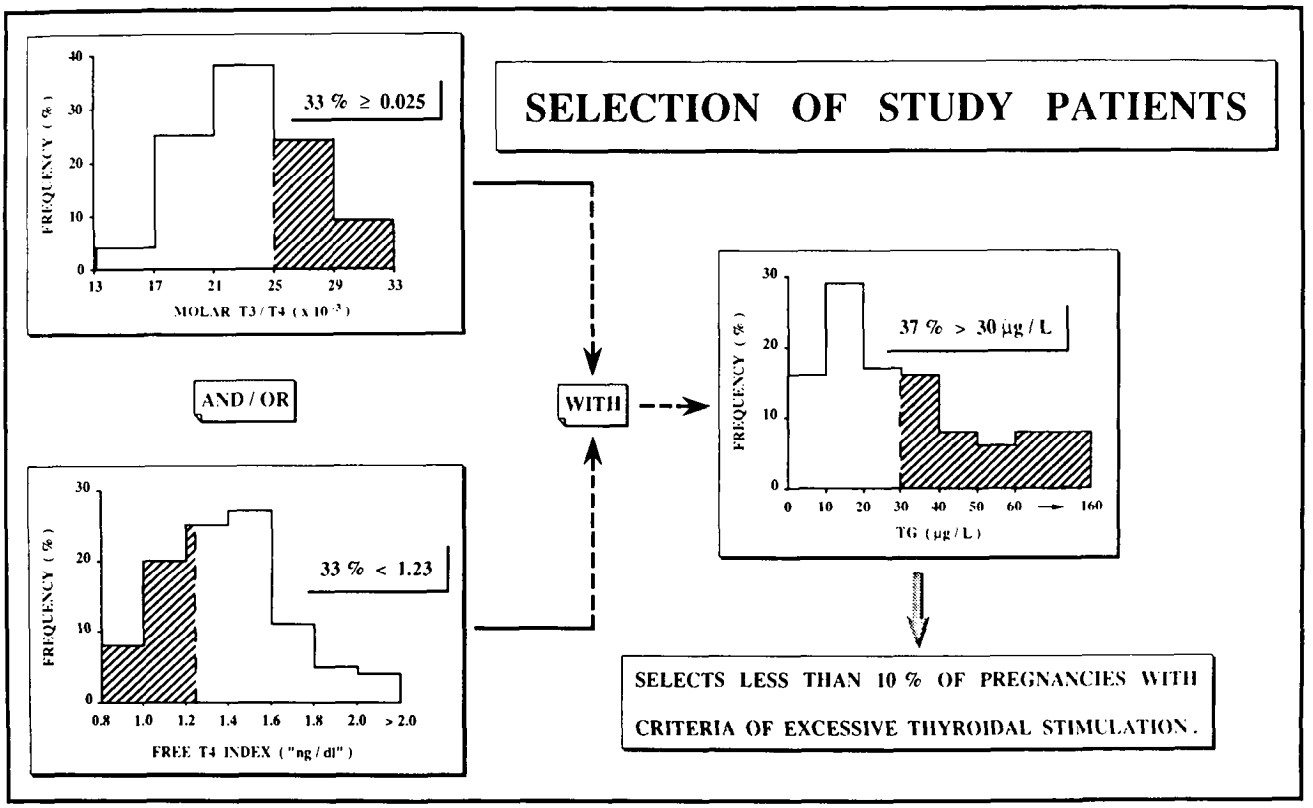

FIG. 1. Distribution frequencies of the molar ratio of T_3/T_4, the free T_4 index, and serum TG levels in the 606 healthy pregnancies reported previously (1). The criteria used for selection of the patients under investigation in the present study were a serum TG level above 20 µg/L together with a molar ratio of T_3/T_4 above 25×10^{-3} and/or a free T_4 index below 1.23. It should be noted that in our earlier work, the upper limit of normality in the TG assay was 30 µg/L; after a change in TG standards in the assay, the upper limit of normality is presently 20 µg/L. One hundred and eighty women of a total of 2000 consecutive pregnancies (9%) met the criteria of selection and constitute the study group. Reproduced with the editor's permission from Ref. 27.

Results

Total T_4 and serum TBG levels

At initial presentation (screening, 10.7 weeks gestation, on the average), total T_4 levels ranged between 65–209 nmol/L, with a mean value of 125 nmol/L. The distribution of serum T_4 values in the population investigated was Gaussian, and there was no difference among the three groups. At the start of therapy (14 weeks gestation), total T_4 had increased significantly by 17%, on the average, to 144 nmol/L ($P < 0.001$, by paired t test). The increase in serum T_4 was parallel to the 20% increase in serum TBG, from 23.4 ± 6.9 mg/L (mean ± SD) to 27.0 ± 6.1 mg/L, resulting from estrogen stimulation. After therapy was started, the patterns of serum T_4 became different in the three groups (Fig. 2). In group A, there was a small further increase in total T_4 levels, averaging 4% and 7%, respectively, during the second and third trimesters. In contrast, in group C, serum T_4 increased significantly more, averaging 19% and 15% above initial values, respectively, during the second and third trimesters. In group B, changes in serum T_4 were intermediate between those of groups A and C, with mean increments of 9% in the second and 11% in the third trimester. Three days after delivery, total T_4 levels were not different among the three groups, and the slight decrease compared to T_4 levels at 32 weeks gestation resulted from both the decrease in serum TBG and the interruption of treatment after parturition. Results for serum TBG are not shown; TBG levels were similar in the three groups throughout gestation and at delivery.

Total T_3 levels and molar ratios of T_3/T_4

The changes in serum levels of T_3 and molar ratios of T_3/T_4 are shown in Fig. 3 as a function of gestation time. At initial presentation, individual T_3 levels showed a wide scatter between 2.2–5.1 nmol/L. Mean serum T_3 was initially similar in all groups (overall mean ± SD, 3.4 ± 0.6 nmol/L). Serum T_3 increased to an overall mean of 3.7 nmol/L, between 10.7–14 weeks gestation ($P < 0.001$, by paired t test). After the start of therapy, there was a further increase in group A, with increments of 7.5% and 5%, respectively, in the second and third trimesters. Changes in serum T_3 were similar in group B, with increments of 7% and 8%, respectively, in the second and third trimesters. In contrast, in group C, serum T_3 showed a gradual and highly significant decrease after the start of therapy. Compared to that in group A, the decrease in T_3 was 9% after 10 weeks of treatment ($P < 0.005$) and 10% in the third trimester ($P < 0.001$). The reduction in serum T_3 in group C was even more pronounced at delivery, with a net difference of 15–18%, compared to groups A and B. In groups A and B, the ratios of T_3/T_4 were supranormal at the start of therapy and remained elevated during gestation. In contrast,

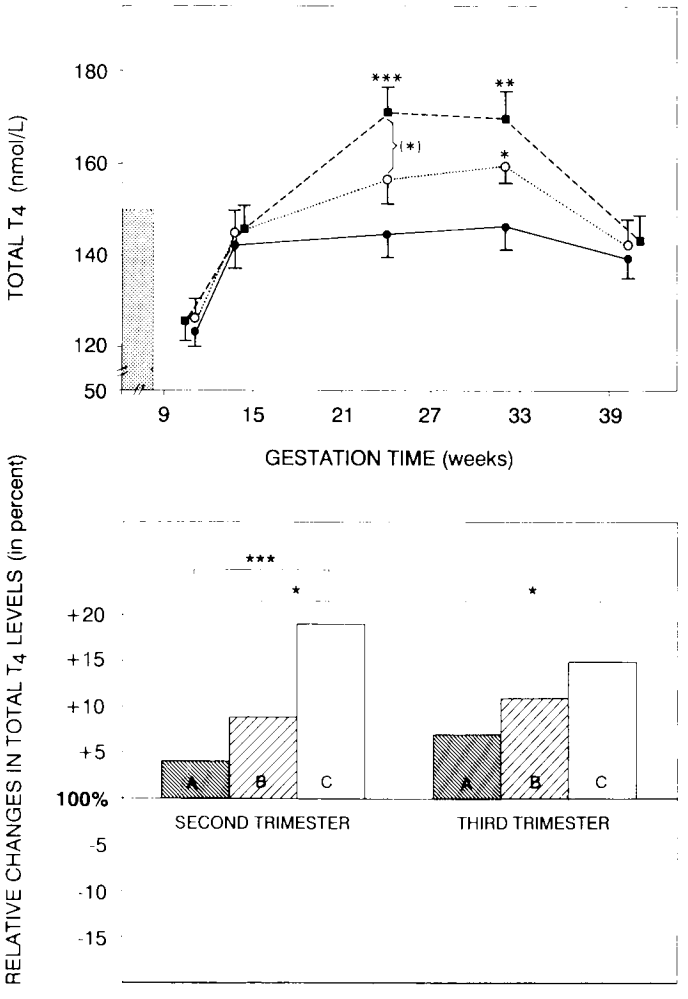

FIG. 2. *Upper graph*, Changes in serum total T_4 levels in groups A (untreated; ●), B (KI; ○), and C (KI plus L-T_4; ■) after the start of therapy. Results are given as the mean ± SEM. The reference range of total T_4 levels in healthy nonpregnant subjects (50–150 nmol/L) is shown as a *shaded area*. Statistical differences were calculated using one-way analysis of variance and are shown for groups B and C in comparison with group A unless otherwise specified on the graph: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$. *Lower graph*. Relative changes in total T_4 levels in the three groups during the study period, expressed as a percentage, compared with values at the start of therapy. Individual ratios were calculated from individual data at each time point divided by data at the start of therapy normalized to 100%; each column shows the mean ratio for each group. Statistical calculations were carried out using nonparametric Mann-Whitney rank sum tests: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

in group C, the ratios of T_3/T_4 decreased rapidly toward normal and were maintained at an overall plateau level of 21–22 × 10^{-3} (Fig. 3). These results indicate that thyroid stimulation associated with pregnancy and leading to preferential T_3 secretion by the thyroid gland was suppressed after KI plus L-T_4 administration.

Free T_4 and TSH levels

The changes in serum levels of free T_4 are shown in Fig. 4 (*left panels*) as a function of gestation time. Free T_4 values were initially normal and comparable in all groups. In groups A and B, free T_4 values decreased gradually during gestation, reaching a plateau near the lower limit of normality, which was maintained until parturition. In group C, in contrast, free T_4 levels increased during treatment and remained significantly higher than those in both groups A and B throughout gestation and at delivery. Figure 4 also shows the mean changes in free T_4 levels, expressed as the percent increment or decrement compared with first trimester data; although the decrement in free T_4 reached 10% in groups A and B, there was a 7–13% increment in group C, *i.e.* a net and highly significant difference of 17–23% compared with the other two groups. Differences between group C and groups A and B were less marked in the days after parturition, because treatment had been withdrawn.

Figure 4 (*right panels*) also shows the changes in serum TSH as a function of gestation time. The pattern of serum TSH was a mirror image of the evolution of serum free T_4 values. Serum TSH rose gradually in group A to eventually reach 2.4 mU/L after delivery, which corresponded to a relative increment of 120%. In group B, serum TSH remained almost stable, but increased by 67% at delivery compared to first trimester data. In group C, TSH decreased after the start of treatment, with a mean decrement of 40% during gestation; at parturition, there was only a 30% increase in TSH values. Scrutinizing individual data for TSH in the three groups yielded interesting information. At delivery, 20% of women in group A had serum TSH levels between 4–6 mU/L, *i.e.* slightly above the upper limit of normality, whereas TSH values above the upper limit of normality were not found in group B or C.

Serum TG levels

Women included in the present trial were selected on the basis of an abnormally elevated serum TG level (Fig. 5). Before the start of treatment, there was no difference in serum TG among the groups, and the overall mean TG level was 43 μg/L. In group A, serum TG remained elevated in the second trimester and rose further in the third trimester (51 ± 3 μg/L; mean increment, 18%) and at delivery (65 ± 5 μg/L; mean increment, 50%). In 14% of women in this group, serum TG doubled between booking and delivery, and 16% of the cases had serum TG values above 100 μg/L (up to 186 μg/L) at delivery. In groups B and C, in contrast, the changes in serum TG after the start of treatment were markedly different. In group B, the mean serum TG level decreased to 26 μg/L in the second trimester and 28 μg/L in the third trimester. In group C, the changes in serum TG were even more pronounced; serum TG decreased to 17 μg/L in the second and 18 μg/L in the third trimester, indicating a normalization of serum TG. Differences between the groups were highly significant.

The *lower part* of Fig. 5 shows the relationship between the relative changes in serum TG and TSH levels for the entire set of patients in the three groups at each time point during gestation. To simplify the presentation, individual results were not plotted, but are symbolized by the mean values calculated in each group at each time point during gestation. The results show that the changes in serum TG (with or

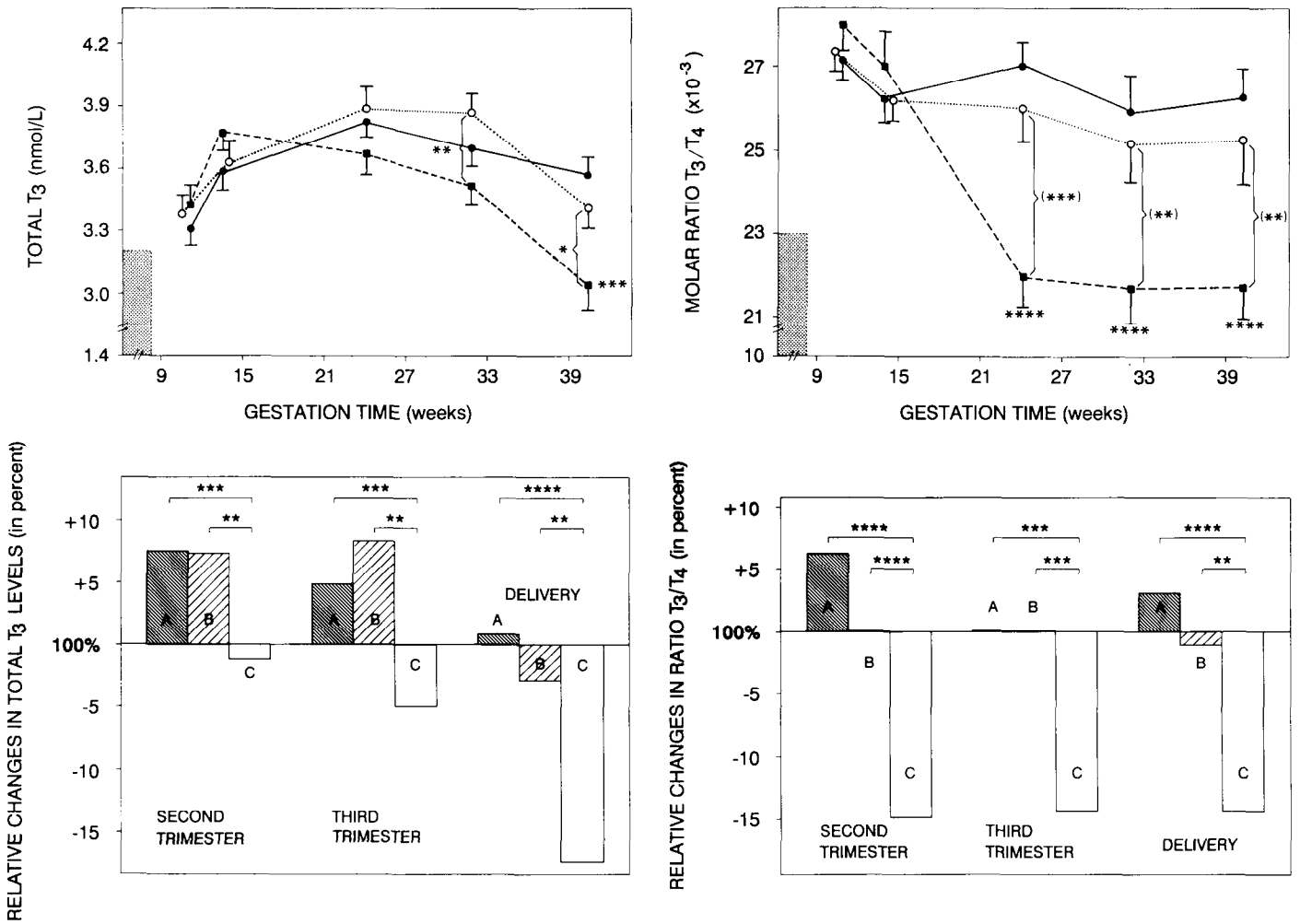

FIG. 3. *Upper graphs*, Changes in serum total T_3 levels and molar ratios of T_3/T_4 in groups A, B, and C after the start of therapy. Same presentation as in Fig. 2. *Lower graphs*, Relative changes in total T_3 levels and molar ratios of T_3/T_4 in the three groups during the study period, expressed as a percentage, compared with values at the start of treatment. Same presentation as in Fig.2.

without active therapy) were highly correlated with the changes in serum TSH.

Iodine status

Changes in urinary iodine excretion levels are shown in Fig. 6 as a function of gestation time. Before the start of therapy, there was no difference among the groups, and the overall median urinary iodine concentration was 36 μg/L. Iodine excretion levels showed a wide individual scatter, with 56% of women below 40 μg/L, 34% between 41–80 μg/L, and only 10% between 81–160 μg/L. After therapy was instituted, the pattern of urinary iodine concentrations was markedly different in both groups B and C compared with that in group A. Although in group A, urinary iodine levels remained extremely low during gestation and at delivery, in groups B and C, urinary iodine concentrations rose significantly in the second and third trimesters. The urinary iodine concentrations were slightly, but not significantly, higher in group C than in group B, but they were significantly higher in both groups B and C compared to group A at all time intervals during gestation. After delivery, when therapy had been withdrawn, urinary iodine levels fell sharply in both groups B and C.

The urinary iodine data were further analyzed in Table 1 from an epidemiological standpoint. In group A, less than 10% of the women had urinary iodine values above 100 μg/L at any time during gestation. In group B, receiving 100 μg I^- daily, the supplementation allowed for 38–50% of the cases to reach or exceed 100 μg/L; in group C, receiving 161 μg I^- daily (from KI and L-T_4), 49–54% of the cases had urinary iodine levels above 100 μg/L. Differences between group A and the other two groups were highly significant, and there was no significant difference between groups B and C.

TV

The overall mean TV at initial presentation was 14.3 ± 0.5 (±SEM) mL. A diffuse goiter (TV >23 mL) was present in 10% of the cases, with TV ranging between 23–64 mL; patients with a goiter at initial presentation were not included in further calculations. For the subjects without a goiter, the main results are presented in Table 2. TV was initially similar in groups A, B, and C. The overall increments in TV between

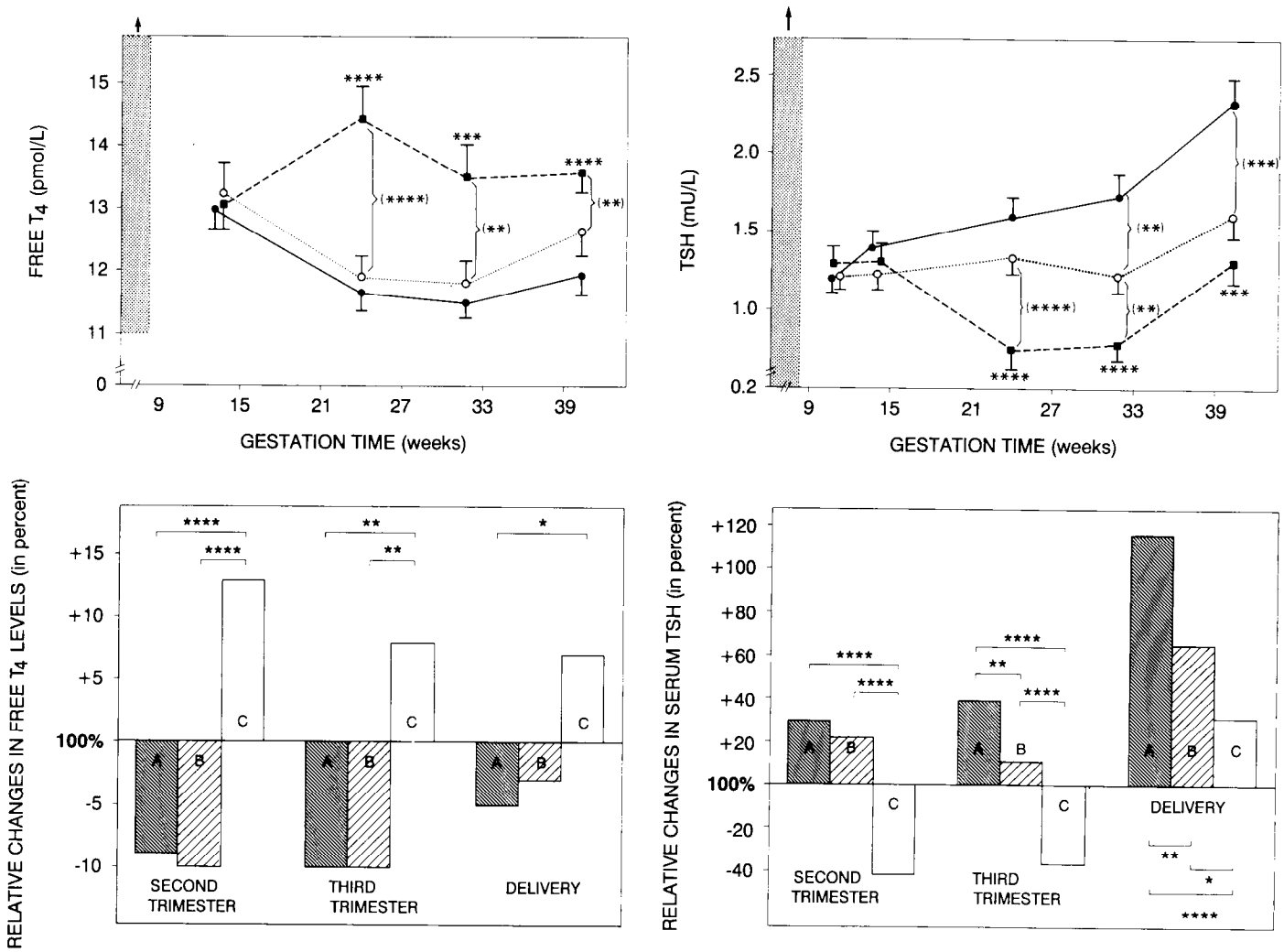

FIG. 4. *Upper graphs*, Changes in serum free T_4 and TSH levels in groups A, B, and C after the start of therapy. For serum TSH, statistical calculations were carried out after log transformation of the data. Same presentation as in Fig. 2. *Lower graphs*, Relative changes in free T_4 and serum TSH levels in the three groups during the study period, expressed as a percentage, compared with values at the start of treatment. Same presentation as in Fig. 2.

initial presentation and delivery were markedly different among the three groups. In group A, TV increased, on the average, by 30%, and 16% of the women in this group developed a goiter during gestation, with TV up to 34 mL at delivery. The increment in TV in group A was significantly greater compared to those in both groups B (mean increase, 15%) and C (mean increase, 8%). Furthermore, goiter formation in groups B and C was less frequent than that in group A, as it was observed in only 10% and 3% of the cases, respectively. We next scrutinized the changes in TV in the three groups. Table 2 presents the percentage of women in each group for whom changes in TV corresponded to an increase (>10%), a decrease (<10%), or the absence of significant change (−10 to +10%). In group A, an increment in TV was present in the majority of cases (74%), but was present in only 35% of the cases in group B and 26% in group C. Conversely, in women of both groups B and C, half of the subjects had no change in TV during gestation, and active treatment actually caused a reduction in TV in approximately 20% of the cases. The differences between changes in TV in group A compared to those in both groups B and C were highly significant; no statistical difference was found between groups B and C.

Changes in TV were also analyzed in relation to serum TG and TSH and urinary iodine concentrations. The results are shown in Fig. 7. When comparing women without a significant change in TV (≤10% increase) or with a TV increment of 10% or more at term, the results indicated that changes in TV were associated with significant differences in both TG and TSH levels, as well as in iodine excretion levels. The highest level of significance was with serum TG, emphasizing the usefulness of serum TG as a marker of goitrogenesis during pregnancy.

Finally, we mentioned that a small number of women who initially had a goiter (n = 17) have not been included in the above calculations. The number of cases was too small in each group to allow statistical analysis. However, scrutinizing individual changes in goiter size as a function of treatment, it was observed that in women who received a placebo, the size of the goiter increased (up to a doubling in volume), whereas in women receiving active treatment, there was in

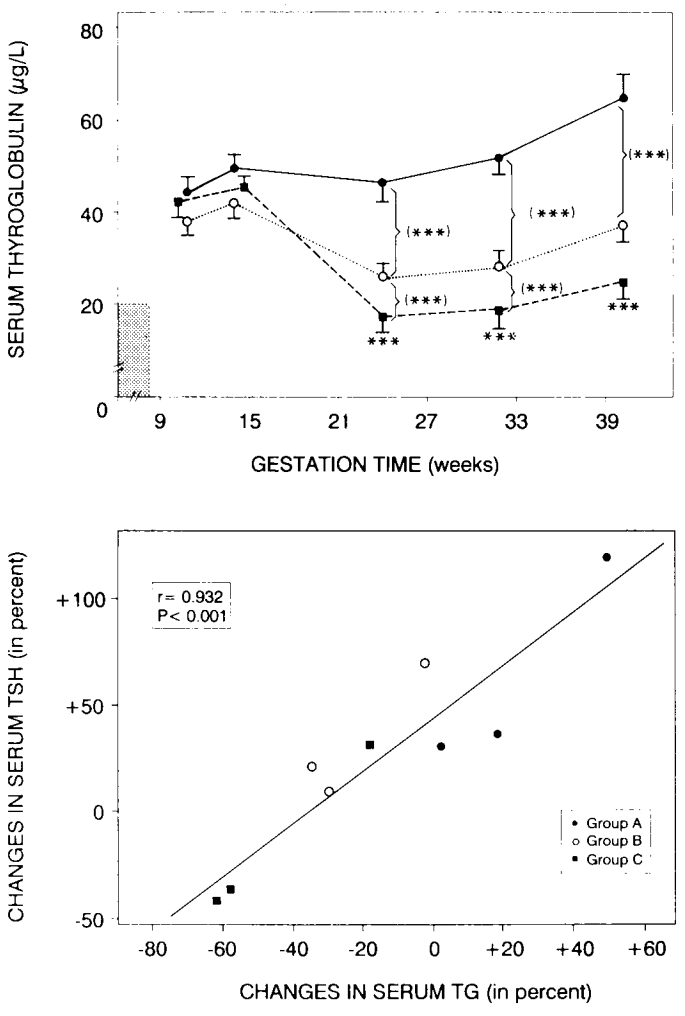

FIG. 5. *Upper graph*, Changes in serum TG levels in groups A, B, and C after the start of therapy. Same presentation as in Fig. 2. *Lower graph*, Relationship between the relative changes (percentage) in serum TG and TSH levels in the three groups at the second and third trimesters and at delivery compared with the results at the start of treatment.

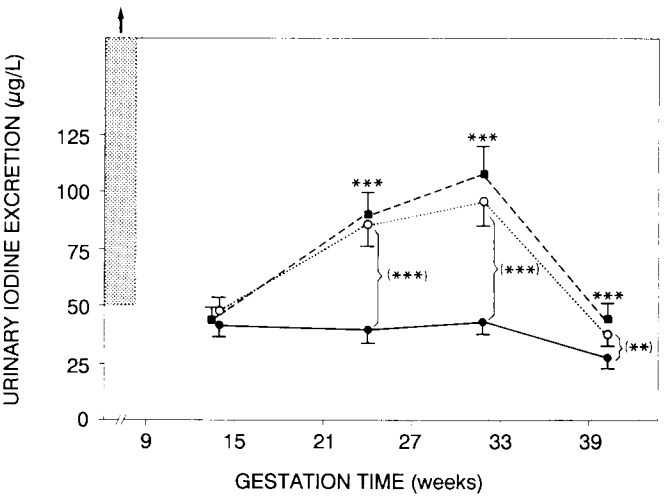

FIG. 6. Changes in urinary iodine concentrations in groups A, B, and C after the start of therapy. Results are given as the mean ± SEM, recalculated after log transformation of the data. Same presentation as in Fig. 2.

TABLE 1. Distribution of urinary iodine concentrations during the study period

Groups	<100 μg/L	≥100 μg/L	χ^2 value	*P*
Before treatment				
A	91	9		
B	87	13	0.9	NS
C	88	12		
Second trimester				
A	94	6		
B	62	38	22.4	<0.0001
C	51	49		
Third trimester				
A	91	9		
B	50	50	20.4	<0.0001
C	46	54		
After parturition				
A	100	0		
B	93	7	3.9	NS
C	93	7		

Results are presented as the percentage of women in each group (A, B, and C) and at each time point. Statistical analysis was carried out using the χ^2 test.

most instances a stabilization or a reduction in the size of the goiter.

Thyroid function parameters in newborns

Results for the newborns are presented in Table 3. Serum levels of total T_4 and T_3, molar ratios of T_3/T_4, TBG, TBG saturation levels, free T_4, and TSH showed no significant difference among the three groups, and the values were within the range of normality for neonatal thyroid function.

For the other parameters, however, important and highly significant differences were observed between neonates born to mothers without treatment (group A) or those receiving active treatment (groups B and C). Mean serum TG was markedly higher in neonates with mothers in group A than in those with mothers in group B or C. Moreover, serum TG levels above 100 μg/L were found in 48% of newborns in group A compared with only 14 and 12% in groups B and C, respectively ($P = 0.0002$, by χ^2 test). Urinary iodine excretion levels and iodine concentrations in breast milk were markedly lower in newborns with mothers in group A than those in newborns with mothers in group B or C. Finally and most importantly, the mean TV in newborns of mothers in group A was significantly larger in neonates of mothers in group A, compared to values in newborns of mothers in both groups B and C; on the average, TV was 38% greater in these babies. Also, glandular hyperplasia (TV >1.4 mL) was found in 10% of newborns in group A (range, 1.5–2.2 mL) compared to none in groups B and C ($P = 0.01$, by χ^2 test).

Discussion

Between 1988–1989, we accomplished our first cohort study on the regulation of thyroid function in pregnancy (1, 5, 26, 27). In that investigation, our goals were to evaluate how the thyroid economy adjusted to the changes associated with pregnancy in an area with a marginally low iodine intake and to assess potential repercussions on maternal and

TABLE 2. Changes in thyroid volume (TV) during pregnancy

Groups	Initial presentation TV (mL)[a]	Overall increment at delivery (%)[b]	Detailed changes in TV at delivery[c]	
A	13.3 ± 0.7	+30 (20–37)	↑ (Δ > 10)	74
			= (Δ −10 to +10)	23
			↓ (Δ < 10)	3
B	13.5 ± 0.7	+15 (4–27)[d]	↑ (Δ > 10)	35[e]
			= (Δ −10 to +10)	48[e]
			↓ (Δ < 10)	17[e]
C	13.0 ± 0.6	+8 (3–13)[f,g]	↑ (Δ > 10)	26[f,h]
			= (Δ −10 to +10)	56[f,h]
			↓ (Δ < 10)	18[f,h]

Ranges (percentages) are given in *parentheses*. Δ, Maximum change.

[a] Mean ± SEM. Values were recalculated after log transformation of the data; women with preexisting goiters (≥23 mL) were excluded from calculations.

[b] Increments in percent compared to TV at initial presentation. Results are expressed as the mean and the 95% confidence interval. Statistical analysis was carried out by one-way ANOVA.

[c] Within each group of women (A, B, and C), changes in volume were classified as an increase of 10% or more (↑) a decrease of 10% or more (↓), or no change (−10% to +10%). Results were expressed as the percentage in each group; statistical analysis was carried out using the χ^2 test.

[d] $P = 0.05$ *vs.* group A.

[e] $P = 0.005$ *vs.* group A.

[f] P = NS *vs.* group B.

[g] $P = 0.001$ *vs.* group A.

[h] $P = 0.0003$ *vs.* group A.

neonatal thyroid function. The study encompassed a total of over 600 healthy euthyroid pregnant women, investigated both cross-sectionally (*i.e.* thyroid function parameters at the initial presentation) and longitudinally (*i.e.* monitoring of thyroid function, iodine excretion, and changes in TV during gestation and up to 12 months postpartum). The study did not include any therapeutic intervention. The results showed that pregnancy in an area with a marginally low iodine intake was associated with significant alterations in thyroid function and specifically that pregnancy induced goitrogenesis and excessive thyroid stimulation in a significant fraction of the women. The main results were 1) relative hypothyroxinemia, evidenced by a less than adequate rise in total T_4 levels (inappropriate for the rise in serum TBG) and the gradual lowering of free T_4 levels during the first half of gestation; 2) preferential T_3 secretion, evidenced by the elevated molar ratio of T_3/T_4; 3) the gradual rise, within the limits of normality, of serum TSH after the first trimester; and 4) a marked elevation in serum TG levels, particularly near term. The rise in serum TG was highly correlated with changes in TV, thereby providing an interesting marker for goitrogenesis occurring during pregnancy (1, 4, 27). Excessive thyroid stimulation was observed in both mothers and newborns. The results led us to conclude that pregnancy constitutes a challenge for both the maternal and fetal thyroid glands, enhanced by the reduced availability of iodine, and to recommend systematic addition of iodine during pregnancy and lactation in our country (1, 6, 10, 20, 27, 28).

The aim of the present study was to evaluate the effects of therapy with iodine alone or iodine combined with L-T_4 on thyroid function in pregnant women who presented in the first months of gestation with biochemical evidence of excessive thyroid stimulation. The following biochemical criteria were considered to establish excessive thyroid stimulation: increased serum TG levels together with an elevated T_3/T_4 ratio and/or a low free T_4 index. Based on the results of our previous study, we knew that such features would be

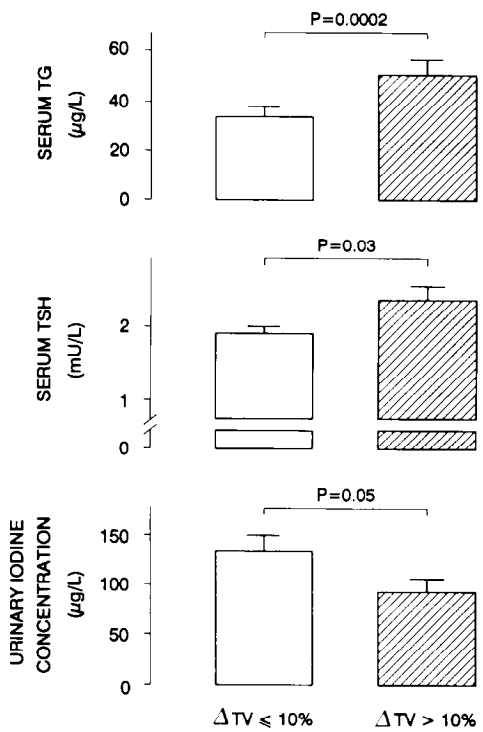

FIG. 7. Comparison of serum TG, serum TSH, and urinary iodine concentrations as a function of changes in TV during gestation. Results are presented as the mean ± SEM. Statistical differences were analyzed by one-way analysis of variance.

expected in less than 10% of all healthy uncomplicated pregnancies presenting at the prenatal clinic. All women with thyroid antibodies and subclinical hypo- or hyperthyroidism were excluded, as were women with a history of thyroid disease or treatment. The present study included 180 selected women with euthyroidism and excessive thyroid stimulation. To reach this sample size, it was necessary to screen 2000 consecutive pregnancies over a period of 30 months. It is

TABLE 3. Neonatal parameters of thyroid function

	Group A	*P* (A *vs.* B)	Group B	*P* (B *vs.* C)	Group C	*P* (C *vs.* A)
Parameters not modified by treatment						
Total T_4 (nmol/L)	141 ± 3	NS	144 ± 5	NS	137 ± 5	NS
Total T_3 (nmol/L)	0.97 ± 0.03	NS	0.95 ± 0.04	NS	0.95 ± 0.05	NS
T_3/T_4 ratio ($\times 10^{-3}$)	7.1 ± 0.3	NS	6.7 ± 0.3	NS	7.3 ± 0.4	NS
TBG (mg/L)	22 ± 1	NS	22 ± 1	NS	22 ± 1	NS
TBG saturation by T_4 (%)	38 ± 1	NS	38 ± 1	NS	36 ± 1	NS
Free T_4 (pmol/L)	14.0 ± 0.5	NS	14.6 ± 0.5	NS	14.3 ± 0.7	NS
TSH (mU/L)	7 ± 1	NS	8 ± 1	NS	8 ± 1	NS
Parameters modified by treatment						
TG (μg/L)	113 ± 9	0.0001	65 ± 6	NS	52 ± 6	0.0001
Urinary iodine (μg/L)	43 ± 4	0.0001	77 ± 8	NS	80 ± 9	0.0001
Iodine in milk (μg/L)	29 ± 2	0.001	61 ± 10	NS	45 ± 5	0.0001
Thyroid vol (mL)	1.05 ± 0.05	0.0001	0.76 ± 0.05	NS	0.75 ± 0.05	0.0001

Results are presented as the mean ± SEM. Statistical analysis was carried out using one-way ANOVA.

TABLE 4. Synopsis of findings

	Group A: placebo	Group B: KI	Group C: KI + L-T_4
Mothers			
Total T_4	→	↑	↑
Total T_3	↑	↑	↓
T_3/T_4 ratio	→	→	↓
Free T_4	↓	↓	↑
TSH	↑	→	→
TG	↑	↓	↓
Urinary iodine	↓	↑	↑
TV	↑	↑	→
Newborns			
Total T_4	Normal	Normal	Normal
Total T_3	Normal	Normal	Normal
T_3/T_4 ratio	Normal	Normal	Normal
Free T_4	Normal	Normal	Normal
TSH	Normal	Normal	Normal
TG	High	Low	Low
Urinary iodine	Low	High	High
TV	Larger	Smaller	Smaller

For mothers, the main findings are symbolized by arrows representing the overall changes during gestation in groups A, B, and C. The direction of the arrow indicates an increase (↑), a decrease (↓), or no significant change (→). For the newborns, the main findings are symbolized by adjectives comparing the data obtained in groups A, B, and C at birth.

important to recognize that the women investigated here do not represent an average pregnant woman, but are a highly selected group, corresponding to the extreme fringe of the normal population. At the start of treatment, the women investigated corresponded by definition to a status of excessive glandular stimulation (median TG, 36 μg/L; molar ratio of T_3/T_4, $>25 \times 10^{-3}$ in 71% of the cases; free T_4 index, <1.23 in 65% of the cases). Euthyroidism was indicated by normal TSH (median, 1.2 mU/L), and the groups were homogeneous with respect to thyroid function parameters as well as clinical parameters (such as age, gravida, para, *etc.*).

The overall results are summarized in Table 4. In the group receiving a placebo (group A), the increase in total T_4 was minimal (<5%) and inappropriate for the rise in serum TBG. Serum T_3 levels, which were already high normal initially, rose further, and the molar ratio of T_3/T_4 remained elevated throughout gestation. Serum free T_4 levels declined gradually to values near the lower limit of normality. Serum TSH levels were, on the average, more than doubled at term compared with TSH in the first trimester. Furthermore, 20% of the women in this group had a supranormal TSH level, and 15% had an infranormal free T_4 level at parturition. Serum TG levels, which were already twice the upper limit of normality initially, increased further, particularly near term. Levels of iodine excretion in the urine were low throughout pregnancy and at delivery; iodine concentrations in breast milk were equally low. Finally and most importantly, changes in TV during gestation were dramatic: an increase in glandular size in three quarters of the cases, an increment in volume averaging 30% of the initial TV, development of a goiter in 16% of women at term, and frequent increases in the size of preexisting goiters. These findings are concordant with our previous observations (1, 4) on the goitrogenic role of pregnancy, amplified in the present study by the selection of the cases. Our data are also in agreement with other investigations on goitrogenesis during pregnancy in areas with a borderline iodine supply. Rasmussen *et al.* (29) reported a 30% increase in TV in 20 unselected pregnancies in Denmark. Pedersen *et al.* (18) made a similar observation of a 31% increase in TV in 26 untreated and unselected pregnancies in another Danish area. Smyth *et al.* (30) found a 15% increase in TV in a cross-sectional study of 25–45 pregnant women in Ireland (where the iodine intake is higher than in Belgium). Romano *et al.* (31) reported a 16% increase in TV between the first and third trimesters in 17 unselected pregnant women in Italy. Similar observations have been made before the era of thyroid ultrasonography, relying on palpation, in areas with known iodine deficiency, such as Scotland (12) and the former East Germany (32). Hypothyroxinemia during pregnancy has also been reported in classical studies, such as those of Silva and Silva in Chile (15) and the late Man *et al.* (33) in the U.S.

At the opposite end of the spectrum, there was the group of women who received KI plus L-T_4 (group C; Table 4). In them, the increase in total T_4 in the first half of gestation was adequate (+15–20%) for the rise in TBG. Despite an increased substrate for T_4 deiodination, serum T_3 levels decreased markedly, as did the molar ratio of T_3/T_4, which, on the average, returned within the range of normal values. Serum free T_4 levels increased by ~10%, with a net difference of over 20% compared to levels in placebo-treated women. Serum

TSH decreased during gestation, compared to initial TSH levels, with only a modest rise at term. Serum TG levels also decreased rapidly with treatment, reverting to normal. The excretion of iodine in urine was more than doubled compared to that in untreated subjects, and breast milk was clearly enriched in iodine. Changes in TV during pregnancy were minimal (<10% increment, on the average), with a stabilization or a reduction in glandular size in the majority of subjects.

Women in this group received 161 μg iodide/day (including, theoretically, the 61 μg derived from L-T_4 catabolism) as well as active thyroid hormone. When we designed the protocol of the trial, there was a logical concern that the beneficial effects of daily iodine supplementation might be hampered by the simultaneous administration of active hormone, because of the potential reduction in iodine uptake by the gland. The results indicate that this was probably not the case, because urinary iodine excretion was only slightly and not significantly higher than that in women who received 100 μg iodide/day. With the combination of KI and L-T_4, hypothyroxinemia and preferential T_3 secretion were abolished, excessive thyroid stimulation improved markedly, and the goitrogenic stimulus of pregnancy was largely suppressed. Changes in TV were reminiscent of the situation reported in the U.S. during pregnancy (13). Furthermore, the beneficial effects of the combined treatment were rapid, with a significant improvement in thyroid function parameters observed after 10 weeks. The combination of KI and L-T_4 is not recommended for all pregnancies in areas with a marginally low iodine supply, but can certainly be proposed for pregnant women who display features of excessive thyroid stimulation in the early stages of pregnancy as well as in women with a preexisting goiter. In the conditions of our investigation, the major benefit from the combined treatment is to rapidly slow down the glandular machinery, which otherwise remains triggered throughout gestation. As far as we are aware, the present study is the first on the use of a combined treatment (KI plus L-T_4) in pregnancy. Using a similar approach, other investigators have reported positive results for the treatment of nontoxic diffuse goiter in areas with a low iodine supply [endemic goiter (34, 35) and juvenile goiter (36, 37)].

The pattern of changes in thyroid function in women who received iodide alone (group B) was intermediate between those in women of groups A and C (Table 4). Serum levels of total T_4 increased in the first half of gestation, although not as much as in group C. Changes in serum T_3 and the ratio of T_3/T_4 were broadly comparable to the values observed in placebo-treated women, even though the T_3/T_4 ratio was slightly less elevated than in group A. Despite the daily addition of KI, free T_4 values declined gradually during gestation (as they did in group A) and were significantly lower than those in group C. However, the benefits of iodine supplementation were evident, as serum TSH remained stable and serum TG decreased significantly, with values for both TSH and TG intermediate between those in the other two groups. Iodine excretion in the urine was more than doubled compared to that in untreated women, and breast milk was enriched with iodine, with iodine levels in milk and urine comparable to those in women of group C. Regarding the changes in TV, the overall increment averaged 15%, intermediate between 30% in group A and 8% in group C, and the goitrogenic stimulus of pregnancy was reduced in the majority of cases. The results can be interpreted as indicating that 100 μg iodide/day were probably not sufficient to reach a stable iodine balance in these highly selected cases. This is understandable because the subjects enrolled in the trial most certainly had low intrathyroid iodine stores resulting from long-standing iodine restriction in the diet (16, 38). Consequently, there was a lag period of approximately one trimester before the benefits of iodine addition were seen. A higher dose of daily iodine might have reduced the lag period or amplified the changes observed. The benefits of iodine supplementation to diminish the goitrogenic stimulus of pregnancy have been reported in two recent case-controlled studies. Romano *et al.* (31) gave iodized salt to 17 unselected pregnant women (120–180 μg iodine/day) and found no change in TV, whereas the TV increment was 16% in the untreated cases. In the study of Pedersen *et al.* (18), our Danish colleagues administered 200 μg iodine/day to 28 unselected pregnant women and reported results similar to those for women in our group B, with a decrease in serum TG, a stabilization of serum TSH, and a significant reduction in the increase in glandular size compared with a control untreated group.

In summary, the overall effects of iodine given alone or combined with L-T_4 were to improve thyroid function parameters and reduce or even suppress the goitrogenic stimulus of pregnancy in women with excessive thyroid stimulation. Differences between the women who received iodine alone or combined with L-T_4 might be attributed in part to differences in the daily amount of iodine received and the necessary lag period when iodine was given alone contrasting with the rapid improvement when active thyroid hormone was added. However, the main difference between the two groups receiving an active treatment was related to the hormonal effect of the addition of T_4.

The last important item concerns neonatal thyroid function. We have previously shown that even in conditions with a restricted iodine intake, pregnancy also constitutes a stimulus for the neonatal thyroid gland, with a parallelism between thyroid stimulation in mothers and that in newborns. It has been shown that under such conditions, newborns are protected from hypothyroxinemia, presumably because maternal iodine available is avidly trapped by the placenta to ensure adequate fetal production of thyroid hormones and perhaps also because of placental transfer of thyroid hormones from the mother to the fetus (6, 39). In the present study, values of total T_4, T_3, and free T_4 were normal for age at birth, and there was no difference in the above parameters between newborns from treated and untreated mothers (Table 4). One striking result, however, also reported recently by Pedersen *et al.* (18), was the significant reduction in serum TG in neonates born to mothers who received an active treatment. Moreover, the most important result of the present study was that the glandular volume was significantly greaterer at birth in newborns from untreated mothers (with thyroid hyperplasia found in 10% of these newborns), whereas in the newborns from mothers receiving an active treatment, the volume was 40% smaller, with no occurrence

of goiter. As there was no difference between newborns in groups B and C, we may assume that iodide supplementation (and not L-T_4) was the key factor allowing the newborns to be protected from goitrogenesis. It is not entirely clear why neonatal TSH values were not different among the groups, but similar findings for TSH have been reported in other studies on neonatal thyroid function in endemic goiter areas (40, 41). Our hypothesis is that TSH at birth does not reliably reflect the process of fetal goitrogenesis, perhaps because this process occurred early during fetal development. One speculation might be that fetal thyroid stimulation in iodine deprivation occurs as early as the thyroid gland starts to develop, leading to a compensatory relative increase in glandular size (corresponding to the early development of a goiter in extreme cases) in a fashion similar to that found in adults submitted to iodine deficiency. One must, therefore, infer that TSH stimulation may have occurred during fetal development, perhaps triggering the role of other growth factors known to be present in large quantities during fetal development.

In conclusion, the present work emphasizes the potential risk of goitrogenic stimulation in both mother and newborn in the presence of mild iodine deficiency. Furthermore, the results indicate the benefits of supplementing pregnant women with iodine and women with excessive thyroid stimulation with a combination of iodine and L-T_4. In conditions of mild iodine deficiency, pregnancy fully justifies the monitoring of thyroid function and volume and therapeutic intervention to avoid hypothyroxinemia and goitrogenesis.

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