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CLINICAL STUDY

Comparison of two different doses of iodide in the prevention of gestational goiter in marginal iodine deficiency: a longitudinal study

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Abstract

Objective: A prospective randomized trial was performed to assess the usefulness of iodine supplementation in the prevention of goiter in pregnant women living in marginally iodine-deficient areas.
Design: Eighty-six pregnant women were recruited and randomized in two groups and treated daily for up to six months after delivery with 200 μg iodide (group A) or 50 μg iodide (group B). Sixty-seven women (32 in group A and 35 in group B) completed the study.
Methods: Thyroid volume (TV), thyroid functional parameters and urinary iodine concentration were determined in all subjects at booking, at the 18th–26th, and the 29th–33rd week of gestation, and at the 3rd and 6th month after delivery.
Results: A slight but not significant increase in TV during gestation was observed only in group B. After delivery a progressive decrease in TV was documented in both groups, the final TV being significantly reduced with respect to the initial volume in group A. No significant changes in serum free thyroid hormones and TSH concentrations were found during gestation in either group. Postpartum thyroiditis was observed in 5 women (2 in group A, 3 in group B). No side effects were seen.
Conclusion: The present data indicate that in marginally iodine-deficient areas, the administration of iodide is recommended in pregnancy and lactation. In the conditions of the present trial a dose of 50 μg iodide/day is a safe and effective measure in preventing an increase in TV during pregnancy but a dose of 200 μg iodide/day appeared to be more effective without inducing side effects and without enhancing the frequency of post-partum thyroiditis.

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Introduction

In iodine-sufficient areas a transient thyroid enlargement during pregnancy may occur, but gestational goiter is rare (1–5). An average 30% increase in thyroid volume in a borderline iodine-sufficient area was reported during pregnancy (6). In iodine-deficient areas pregnancy is frequently accompanied by an increase in thyroid volume with a high prevalence of goiter (7–12). The main mechanism of goitrogenesis in pregnancy is increased glomerular filtration rate with an increased renal loss of iodine from early pregnancy (13–14): the resulting increased requirements of iodide enhance environmental iodine deficiency (15–19). An additional mechanism of iodine loss occurs in the second half of gestation, due to the passage of a fraction of iodine from the maternal circulation to the fetal–placental complex (17). Many studies carried out in severe and mild iodine-deficient areas demonstrated the efficacy of iodide supplementation in preventing the increase in thyroid volume during pregnancy and after delivery when compared with placebo or no treatment (20–23). Scanty data are available on the usefulness of iodine supplementation in marginal iodine deficiency. To study this problem a prospective randomized trial with two different daily doses (50 μg vs 200 μg) of iodide has been performed in pregnant women living in a marginally iodine-deficient area of Italy.

Subjects and study design

Eighty-six consecutive unselected pregnant women whose ages ranged from 20 to 38 years (mean 31 years) were enrolled from the 10th to the 16th week of gestation, between February 1995 and March 1998. The protocol was approved by the Ethical

Committee of the Faculty of Medicine of the University of Pisa and an informed consent was required. A detailed history to exclude past or present thyroid disease, recent exposure to iodine, intake of goitrogenic drugs and thyroid hormones was collected. The women with clinical and laboratory evidence of hyperthyroidism, hypothyroidism, thyroid autoimmunity (thyroid autoantibodies $>1{:}400$) or thyroid volume greater than 20 ml were excluded. After recruitment, 7 women withdrew their consent and 12 dropped out of the study. Eight of these twelve women discontinued the study prematurely for serious gestational events (hyperemesis gravidarum, miscarriage, abruptio placentae, premature delivery); 67 pregnant women completed the study. Five developed post-partum thyroiditis and were separately considered after delivery.

The study was designed as a prospective, randomized, open label trial. The trial medication was provided by Merck KgaA (Iodid 200, containing 261.6 μg potassium iodide equivalent to 200 μg iodide, and Iodid 100, containing 130.8 μg potassium iodide equivalent to 100 μg iodide). The 67 women were randomly subdivided into two groups. Thirty-two subjects (group A) received 200 μg iodide/day and 35 subjects (group B) received 50 μg iodide/day (1/2 tablet of Iodid 100). Treatment was given from the day of recruitment up to six months after delivery. Thyroid volume (TV), serum free thyroxine (T_4) and free triiodothyronine (T_3), serum thyrotropin (TSH), serum thyroglobulin (Tg), anti-thyroglobulin (TgAb) and anti-thyroperoxidase (TPOAb) antibodies, and urinary iodine concentration were determined in all subjects at booking, at the 18th–26th week, at the 29th–33rd week of gestation (pre-partum), and at the 3rd and 6th month after delivery. We did not have a control no-treatment group due to non-approval by the Ethical Committee.

Methods

Serum free T_4 (FT_4) and serum free T_3 (FT_3) were measured by RIA (FT_4 Lyso-Phase kit; FT_3 Lyso-Phase kit; Technogenetics, Milan, Italy). The normal range was 6.5–18 pg/ml for FT_4 and 2.3–5.5 pg/ml for FT_3. Serum TSH was determined by an ultrasensitive immunoradiometric assay (Gamma Coat 125-I, Incstar Corp., Stillwater, MN, USA) with a detection limit of 0.4–3.8 μU/ml. Serum Tg was determined by IRMA (Thyroglobuline IRMA Pasteur, Sanofi, France). Serum autoantibodies to thyroglobulin (TgAb) and thyroperoxidase (TPOAb) were measured by agglutination (Serodia-ATG and Serodia-AMC, Fujirebio Inc., Tokyo, Japan). The urinary iodine concentration was assessed on casual urinary samples by a colorimetric method using an autoanalyzer apparatus (Technicon, Rome, Italy) and expressed as median value. The results were calculated as μg iodine/g creatinine. The intra- and interassay coefficients of variation for determination of urinary iodine excretion (UIE) were $<10\%$. Thyroid ultrasound examination was performed with a portable real-time instrument (Esaote, Biomedica, Firenze, Italy) using a 7.5 MHz linear transducer. Thyroid volume was calculated according to the formula of the ellipsoid model: width × length × thickness × 0.52 for each lobe (24). The coefficient of variation for determination of TV was estimated to be $<10\%$.

Statistical assessment

Data for TV, FT_4, FT_3, TSH were given as means±S.E. Statistical analysis of the data was performed using unpaired *t*-test and Chi-square test. Significance was defined as $P < 0.05$.

Results

Table 1 shows the initial values of thyroid volume, urinary iodine concentration, serum FT_4 and FT_3, serum TSH and serum Tg in the two groups of pregnant women.

Urinary iodine excretion (UIE)

The median UIE in the whole series was 74 μg/g creatinine. After randomization, the median UIE was 91 μg/g creatinine in Group A and 65.5 μg/g creatinine in Group B. At the pre-partum interval UIE was 230 μg/g creatinine in Group A and 128 μg/g creatinine in Group B. Six months after delivery UIE was 156 μg/g creatinine in Group A and 123 μg/g creatinine in Group B. Urinary iodine concentration rose during gestation and the post-partum period in both groups. A significant difference ($P < 0.0001$) at the pre-partum interval between the two groups was found. The percentage of women with urinary iodine levels above 100 μg/g creatinine rose during iodide supplementation, from 44% to 93% in group A and from 34% to 66.6% in group B, with a significant difference between the two groups ($P < 0.01$).

Table 1 Values for thyroid volume, urinary iodine excretion, serum free T_4 and free T_3, serum TSH and serum Tg at initial visit in the two groups of pregnant women. Values are expressed as means±S.E.

	TV (ml)	**UIE** (μg/g cr)	**FT_4** (pg/ml)	**FT_3** (pg/ml)	**TSH** (μU/ml)	**Tg** (ng/ml)
Group A	11.3±0.8	116±14	10.4±0.3	3.1±0.09	1.1±0.08	25±5.6
Group B	11.2±0.5	97±12	10.1±0.4	3.0±0.1	1.1±0.1	24±8.0

Cr, creatinine; TV, thyroid volume; UIE, urinary iodine excretion.

Thyroid volume

No woman in our series developed goiter during pregnancy. Thyroid volume was 11.3±0.8 ml (mean±S.E.) in group A and 11.2±0.5 ml in group B at the first interval. At the pre-partum interval, TV was 11.6± 1.0 in Group A and 12.3±0.7 in Group B. Six months after delivery, TV was 10.7±0.9 in Group A and 10.4±0.6 in Group B. Changes in TV during treatment are shown in Fig. 1. During treatment, no difference was found between the two groups at each time interval. A slight but not significant increase in TV during gestation was observed only in group B. Half of the women in group A and 36% of the women in group B had no change in TV during gestation. An increase higher than 10% in TV was observed in 33% of women in group A and in 55% of women in group B. After delivery a decrement in TV was present in 18.5% of the subjects in group A but only in 9% of the subjects in group B. Only in Group A was the final TV significantly lower than in the first interval.

Thyroid function

Changes in serum FT_4 and FT_3 levels during treatment are shown in Fig. 2 (upper panels). Both FT_4 and FT_3 values decreased during gestation, remaining in the normal range and reaching a plateau in the second half of gestation in both groups. After delivery, both FT_4 and FT_3 concentrations progressively increased, reaching comparable levels to those of the first visit in both groups. No difference was found between the two groups at each time interval during gestation and after delivery. Changes in serum TSH and serum Tg levels during treatment are shown in Fig. 2 (lower panels). No significant change in serum TSH and serum Tg concentrations at each time interval during gestation and after delivery was observed in both groups. At booking, 10 women showed low titers of Tg and/or TPO autoantibodies which did not increase during iodine supplementation.

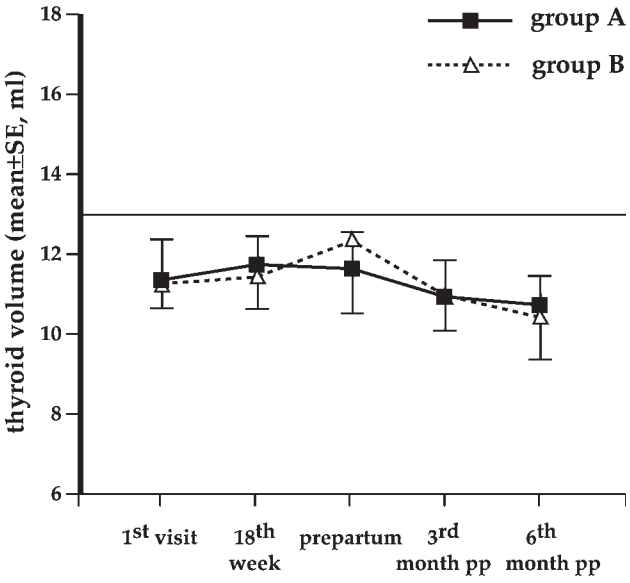

Figure 1 Thyroid volume during pregnancy and after delivery at each time interval in women receiving a dose of 200 μg iodide/day (group A) and 50 μg iodide/day (group B). No difference was found between the two groups at each time interval. First visit was between 10–16 weeks of gestation. pp, post-partum.

Clinical events

Post-partum thyroiditis was observed in 5 women (2 in group A and 3 in group B, 8.5% of whole series), occurring strictly in the fraction of women with pre-existing low titer of circulating thyroid autoantibodies. All had a transient phase of biochemical hyperthyroidism without clinical signs or symptoms of thyrotoxicosis, followed by subclinical or clinical hypothyroidism six months or more after delivery. In four cases, hypothyroidism was transient whereas in one case hypothyroidism was permanent. No side effects related to iodine supplementation were observed in our series.

Discussion

Our series of pregnant women were living in an area of Italy characterized by marginal iodine deficiency as indicated by the urinary iodine excretion. A stabilization or a decrease in TV at the pre-partum interval was found in two thirds of women treated with 200 μg iodide/day (group A) while the remaining subjects showed a negligible increase in TV. This result is in agreement with a report on the effects of iodized salt supplementation with similar doses of iodide in pregnant women living in moderately iodine-deficient areas (20). In the women treated with 50 μg iodide/day a stabilization or a decrease in TV during gestation was present in 45% of women while over half of the subjects showed a slight increment in TV, associated with no significant increase in serum Tg concentration. Similar results were observed by Glinoer *et al.* (22) in 60 pregnant women living in a moderately low iodine-deficient region and receiving 100 μg iodine/day. This result may be interpreted as indicating that 100 μg iodine/day or less are not sufficient to completely prevent the goitrogenic stimulus of pregnancy in conditions of borderline iodine intake (22). In keeping with other authors (21), the continuation of iodide supplementation during the post-partum period determined a progressive decrease in thyroid volume in both groups in our study and the final TV was slightly lower than that at the initial interval only in women receiving 200 μg iodine/day. On the contrary, in untreated women in whom TV was significantly increased during pregnancy, TV did not completely revert to the initial value after delivery (25). These

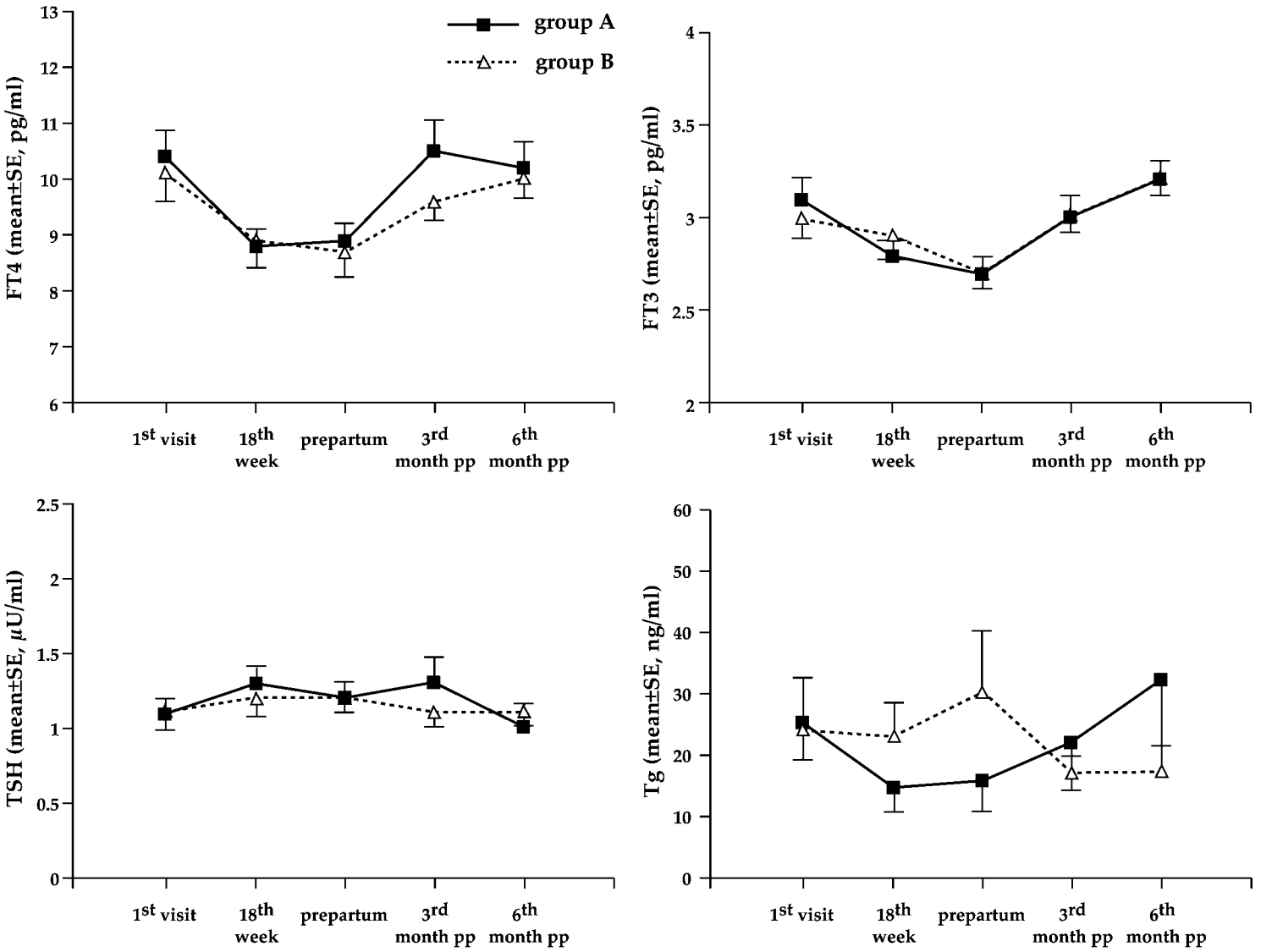

Figure 2 Changes in serum levels of FT_4, FT_3, TSH and Tg at each time interval during pregnancy and after delivery in the two groups. No difference was found between the two groups at each time interval. First visit was between 10–16 weeks of gestation. pp, post-partum.

findings suggest that the modifications in TV are related to iodine availability.

In both groups in our study, serum FT_4 and FT_3 concentrations decreased during gestation, remaining in the normal range with no significant change in serum TSH concentration. This trend was similar to that reported in untreated pregnant women living in iodine-sufficient areas (5) and in pregnant women living in iodine-deficient areas and supplemented with iodide (21, 22). In untreated (15, 22, 26, 27) or placebo-treated pregnant women living in mildly iodine-deficient areas an increase in TV associated with a decrease in serum free thyroid hormone concentration and an increase in TSH was documented (21). An increase in TV with unmodified TSH levels was reported also in untreated pregnant women living in iodine-deficient areas (20).

In our series a post-partum thyroiditis occurred in 8.5% of cases. This prevalence is similar to that observed in the general pregnant population, independent of iodine intake and iodide supplementation (28–32). However, to detect the real incidence of thyroiditis post-partum a higher number of observations is needed. Hypothyroidism developed in all cases of post-partum thyroiditis and was transient in 4 cases with recovery of thyroid function within 1 year post-partum. In our conditions iodide supplementation does not induce an enhancement of the prevalence of post-partum thyroiditis. In agreement with other studies, all our cases of post-partum thyroiditis occurred in the subgroup of women with pre-existing low titers of circulating thyroid autoantibodies (31–34).

In conclusion, the present data indicate that in marginally iodine-deficient areas, the administration of iodide is recommended in pregnancy and lactation. In the conditions of the present trial both doses of iodide are safe and effective measures in preventing an increase in TV during pregnancy without inducing side effects and without enhancing the frequency of post-partum thyroiditis. However, the women treated with 50 μg iodide/day had a median UIE of 128 μg/g creatinine at the pre-partum interval, a value lower than that suggested by the World Health Organisation during pregnancy (35). As reported by other authors, pregnancy increases the maternal requirement for iodide caused by the increased renal clearance of iodide from the kidney. Increased urinary iodine loss during pregnancy may underestimate the prevalence of iodine deficiency during pregnancy (6, 10).

Therefore a daily dose of 200 μg iodide appeared to be more effective in preventing thyroid enlargement.

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