

Amelioration of Some Pregnancy-Associated Variations in Thyroid Function by Iodine Supplementation*

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ABSTRACT

Knowledge of the effect of differences in iodine intake levels on public health in areas with no endemic goiter is limited. Groups at risk when iodine intake is relatively low are pregnant and lactating women and their newborns. A prospective randomized study was performed to evaluate the effect of iodine supplementation in an area where the median daily iodine excretion in urine is around 50 μg .

Fifty-four normal pregnant women were randomized to be controls or to receive 200 μg iodine/day from weeks 17–18 of pregnancy until 12 months after delivery. In the control group, serum TSH, serum thyroglobulin (Tg), and thyroid size showed significant increases during pregnancy. These variations were ameliorated by iodine supplementa-

tion. Iodine did not induce significant variations in serum T_4 , T_3 , or free T_4 . Cord blood Tg was much lower when the mother had received iodine, whereas TSH, T_4 , T_3 , and free T_4 levels were unaltered.

The results suggest that a relatively low iodine intake during pregnancy leads to thyroidal stress, with increases in Tg release and thyroid size. However, the thyroid gland is able to adapt and keep thyroid hormones in the mother and the child normal, at least under normal circumstances, as evaluated in the present study. It is not known whether this stress is sufficient to be of importance for late development of autonomous thyroid growth and function. (*J Clin Endocrinol Metab* 77: 1078–1083, 1993)

IODINE intake levels vary considerably in different parts of the world. In areas with a very low iodine intake, a high frequency of goiter in young subjects is a prominent finding. Such endemic goiter indicates that an iodine supplementation program should be initiated. A more serious consequence of iodine deficiency, cretinism, is an indicator of the urgent need for iodine supplementation (1). The opposite situation, with a high frequency of disease in an area due to a very high iodine intake, is much less common. In certain areas of Japan with a very high consumption of iodine-containing seaweed (2) and of China with a high iodine content in water (3), high frequencies of iodine-induced goiter have been described.

When no endemic goiter is found, iodine intake is considered to be sufficient, and knowledge concerning the effects of differences in iodine intake in such areas is limited. In our area, Denmark, iodine intake has been stable low for many years, but no endemic goiter is found (4–8). This is similar to the situation in a number of other European countries (9).

It has been considered to increase the iodine intake in Denmark, but the consequences of this are only partly known. Comparative epidemiological studies of the incidence of various types of hyperthyroidism in our area and a comparable area with a stable high iodine intake (Iceland)

suggest that a considerable shift in types of thyroid diseases and the age at which they manifest could be induced (10).

However, even if no obvious signs of iodine deficiency are observed in the population, it is possible that iodine deficiency could exist in certain groups or during certain periods of life, and that this could lead to unnecessary morbidity. During pregnancy and lactation, iodine requirements are higher than normal (11), and sufficient iodine for synthesis of thyroid hormone is important for normal brain development (12). Hence, pregnant and lactating women and their newborns are special groups at risk in areas with a low iodine intake (13). In a previous study we found a high serum thyroglobulin (Tg) level in pregnant women near term (14). This could be due to the increase in the iodine requirement during pregnancy, which was not met in these women (15). Such a mechanism could also be involved in the increase in thyroid size during pregnancy observed in some (16–19), but not in all (20), studies. In a previous longitudinal study of normal pregnant women, we found an increase in serum TSH and a fall in serum free T_4 in late pregnancy (21), as has been reported by other investigators (22). Such a variation is also compatible with iodine deficiency.

We have now investigated, in a prospective randomized study, the consequences of iodine supplementation during pregnancy and the first year postpartum on the thyroid function of women and their newborns.

Subjects and Methods

This investigation was performed in the commune of Randers, East Jutland, Denmark. In this area, the urinary excretion of iodine is around

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50 µg/day (8, 14). The participants in the study were 54 normal pregnant caucasian women attending the out-patient clinic of the Department of Obstetrics and Gynecology, Randers Centralsygehus, early in pregnancy as part of local routine. None had previous thyroid disease, and none took iodine supplementation or medication that could affect thyroid function.

Initially, 74 women were willing to participate; however, after the first visit 20 women left the study, mainly because they felt that it would interfere with their jobs. Of the remaining 54 pregnant women, 26 were controls and 28 were randomized to iodine supplementation by a daily intake of 10 drops of a KI solution (200 µg iodine) from the 17–18th week of pregnancy until 12 months after delivery. All 54 pregnant women were followed at regular intervals during pregnancy. During the year after delivery, 5 women left the area (3 from the iodine supplementation group and 2 from the control group). They were excluded from the postpartum part of the investigation. Nine women in the group with iodine supplementation and 7 in the control group were cigarette smokers. Data on the women participating are shown in Table 1.

Thyroid volume was measured by sonography at 17–18, 28, and 37 weeks of pregnancy and 5 days and 26 and 52 weeks after delivery, as previously described (14), using the method described by Bruun *et al.* (23). A General Electric Ultrasonic Scanner (type RT 3000) (Rancho Cordova, CA) with a 5-mHz linear transducer was used. The volume was estimated by multiplication of length, width, and thickness and a corrective factor (0.479) for each thyroid lobe. All measurements were performed three times for each lobe, and the average value was calculated. The measurements were performed by two experienced investigators. The investigators performing the volume measurements did not know which subjects received iodine or the results of previous volume determinations. Interobserver variation was previously found to be 13% (17). In three women (two control and one iodine supplemented), thyroid volume was not measured immediately before delivery. For calculation of the 37 week gestation values, the values obtained 1 week after delivery were used. One woman in the control group could not afford the time for the investigation 26 weeks after delivery.

Blood and urine samples for analyses were obtained at the time of measurement of thyroid volume and 13 and 39 weeks after delivery. Blood samples were obtained between 0900–1500 h. A morning spot urine sample was collected and sent to the laboratory. The urine sample at 52 weeks postpartum was collected after the participants had stopped taking iodine. Serum and urine samples were kept at –20 C until analyses. Breast milk and urine from the newborn were collected on day 5 after delivery. Sera from cord blood, milk, and urine were kept at –20 C.

Iodine in urine and milk was measured in duplicate by the Ceri/Arsenium method after alkaline ashing by a modification of the method of Wilson and van Zyl (24), as described in detail previously (25). The lowest standard contained 10 ng/mL iodine. The response to this standard was always considerably higher than that to the zero standard. Recovery of added ¹²⁷I and ¹²⁵I was above 95% and was not corrected

for. Total T₄ in serum was measured by an in-house RIA, total T₃ by a RIA from Farnos (Turku, Finland), and free T₄ by a two-step analog method (RIA-gnost FT₄, Behringwerke, Marburg, Germany). Serum Tg was measured by an immunochemiluminiscense method (Behringwerke). This method includes measurement of the recovery of added Tg. Results from two women (one from each group) were excluded because the recovery was markedly outside the range of acceptance (80–120%). Thyroid peroxidase (TPO) antibodies in serum were measured by enzyme-linked immunosorbent assay (26).

Statistical analyses were performed using the Medstat program version 2.12 (Astra, Albertslund, Denmark), employing nonparametric tests (calculation of median, 95% confidence limits of median, Mann-Whitney test, Friedman test, and Friedman test with multiple comparisons between conditions) (27).

Results

Before iodine supplementation was initiated, the measured variables were nearly identical in the two groups of pregnant women (Table 1). The initial serum T₄ and T₃ levels were high, corresponding to weeks 17–18 of pregnancy (21). Only small and nonsignificant variations in serum T₄ and T₃ were observed during pregnancy, with no statistically significant difference between the two groups of women (Fig. 1). Corresponding to this, no significant variations or differences in the T₄/T₃ ratio were observed (Fig. 1). After delivery, both T₄ and T₃ in serum showed a fall, as expected, with no difference between the groups. In the sample obtained on day 5 after delivery, serum T₃ was relatively low compared to serum T₄ (Fig. 1). This was possibly part of an immediate postpartum low T₃ syndrome.

Serum free T₄ showed a significant decrease during pregnancy in both groups, with no significant difference between the groups (Fig. 1). After delivery, an increase in free T₄ was observed.

The most prominent variation observed was that in serum Tg (Fig. 2). In the control group, serum Tg showed an increase, with high levels around delivery. The values returned to initial levels during the postpartum period. Iodine supplementation abolished the increase in Tg, which began to decrease. The level remained below the control level during the entire study period and was eventually reduced to 41% of the initial value (Fig. 2).

Serum TSH (Fig. 2) showed a gradual moderate increase during pregnancy in the control group to 121% of the initial value. In the iodine-supplemented group, such an increase in serum TSH during pregnancy was not observed (Fig. 2). After delivery, a gradual decrease in serum TSH was observed in the control group, whereas more irregular variations were observed in the iodine-supplemented group.

Figure 3 depicts the median variation in thyroid size. In the control group, a significant increase of 30.8% in thyroid size was observed during pregnancy. Iodine supplementation caused a significant reduction (*P* < 0.02) in this increase to a median of 15.5%. During the postpartum period, a reduction in thyroid size was observed in both groups, and 12 months after delivery, the values were very close to the initial values [control group, 105.4% of the initial value; iodine-supplemented group, 106.0% of the initial value (median)].

The intake of iodine was semiquantitatively assessed by measuring iodine in a spot urine sample (Fig. 4). As the

TABLE 1. Data on pregnant women at initial visit

	Iodine-supplemented	Controls
No.	28	26
Age (yr)	25.0 (24–27)	26.3 (25–29)
BW (kg)	61.9 (58.5–67.2)	64.0 (59.5–70.0)
Parity	1.3 (1–2)	1.5 (1–2)
Smokers (n)	9	7
Thyroid vol (mL)	9.6 (7.6–10.6)	9.5 (7.1–11.0)
Serum TSH (mU/L)	1.63 (1.28–1.91)	1.43 (1.03–1.87)
Serum Tg (µg/L)	11.5 (6.0–17.0)	10.8 (7.8–24.0)
Serum T ₄ (nmol/L)	169 (160–184)	178 (161–207)
Serum T ₃ (nmol/L)	2.05 (1.86–2.29)	2.22 (1.88–2.60)
Serum free T ₄ (pmol/L)	10.5 (9.1–11.6)	11.1 (9.5–11.6)
Serum T ₄ /T ₃	77 (68–89)	79 (72–91)
Urinary iodine (µg/L)	55 (30–73)	51 (32.0–58.0)

Data [median (95% confidence interval)] from pregnant women randomized to the presence or absence of iodine supplementation (200 µg/day) during pregnancy and 1 yr after delivery.

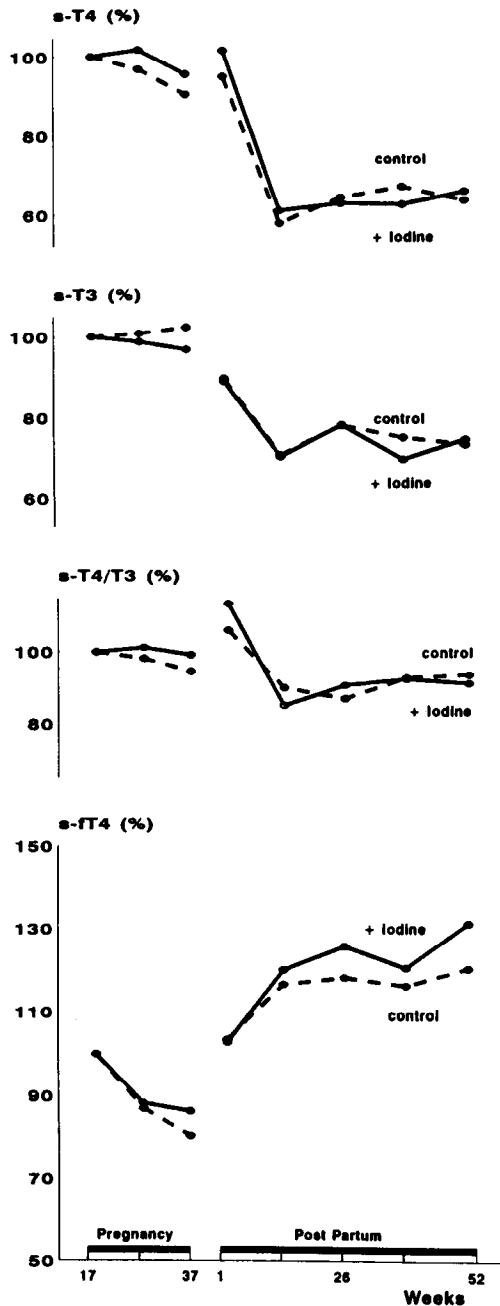


FIG. 1. Serum T_4 and T_3 , the ratio between T_4 and T_3 , and serum free T_4 during pregnancy and for 52 weeks postpartum in women receiving iodine supplementation and control women. All values were expressed as a percentage of the value obtained before iodine supplementation. The absolute initial values are given in Table 1. The curves are median values. The variations in serum T_4 and serum T_3 during pregnancy were not statistically significant. The ratio between T_4 and T_3 showed a significant increase in both groups on day 5 after delivery compared to both the last value during pregnancy and the value 3 months after delivery ($P < 0.05$). The decrease in serum free T_4 during pregnancy was statistically significant ($P < 0.0001$ in both groups). No significant differences between groups were observed.

interval between the daily iodine administration and the sampling was not fixed, the values observed cannot be used to evaluate the iodine balance in detail. As expected, an

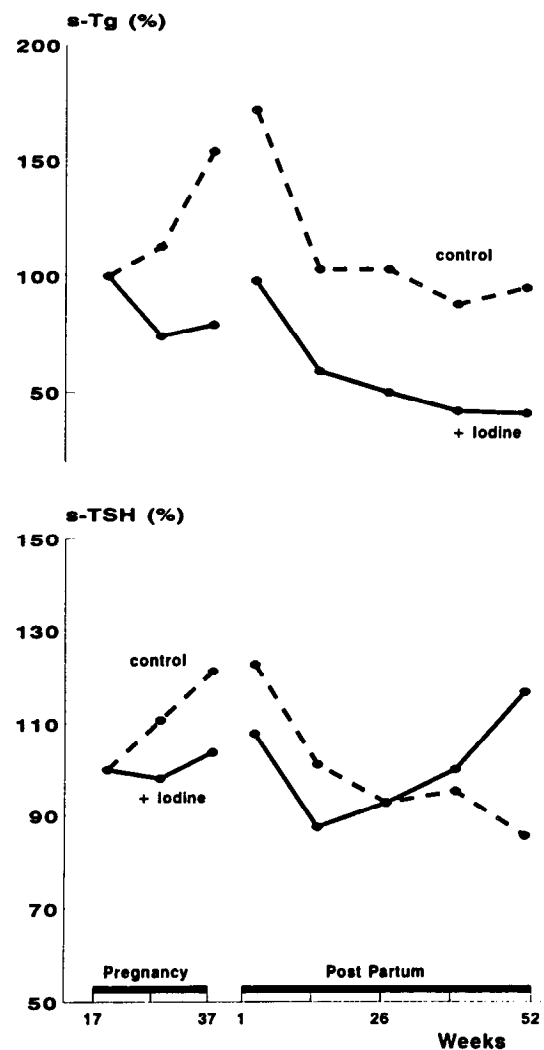


FIG. 2. Serum Tg and serum TSH during pregnancy and for 52 weeks postpartum in women receiving iodine supplementation and control women, as a percentage of the initial values (see Table 1). Median values are shown. The increase in serum Tg during pregnancy in the control group was statistically significant ($P < 0.01$), but the first value obtained during pregnancy and the values obtained 1 yr after delivery were not different. In the iodine-supplemented group, the falls during pregnancy and after ($P < 0.001$) pregnancy were significant. Tg values from the two groups were significantly different at all periods, except before initiation of iodine supplementation. In the control group, the increase in TSH during pregnancy was statistically significant ($P < 0.01$), whereas no difference between values were found in the iodine-supplemented group ($P = 0.29$, by Friedman's test). During the postpartum period, no significant TSH differences between the groups were found.

increase in urinary iodine was observed in the women taking iodine. The values were relatively low in both groups in the first sample after delivery. In the last sample obtained after cessation of iodine intake, no difference between groups was observed (Fig. 4). The effects of iodine supplementation on the iodine content of breast milk and the urinary iodine concentration of the child on day 5 after delivery are shown in Table 2.

Table 3 shows the results of measurements of cord blood. TSH, T_4 , T_3 , and free T_4 values were similar in the two

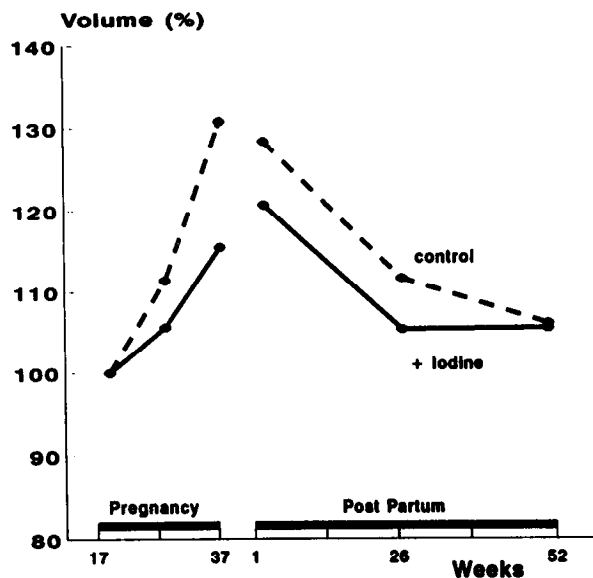


FIG. 3. Median thyroid volume during pregnancy and for 52 weeks postpartum in women receiving iodine supplementation and control women, as a percentage of the initial values (see Table 1). In both groups, significant increases during pregnancy and decreases during the postpartum period were found ($P < 0.05$). The increase during pregnancy in the control group was higher than that in the iodine-supplemented group ($P < 0.05$).

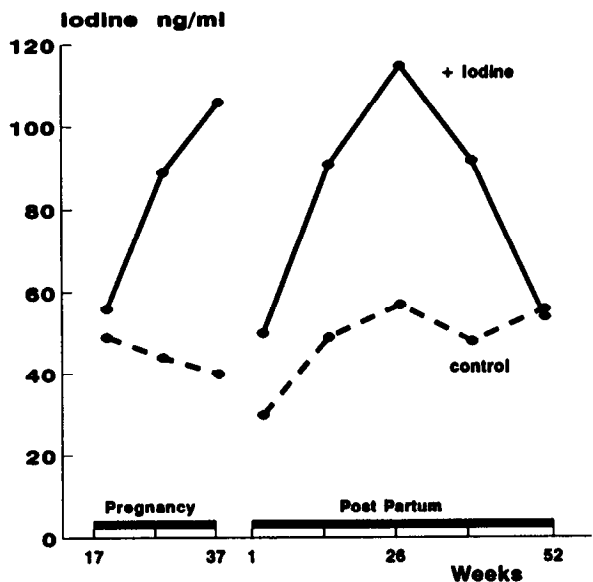


FIG. 4. Iodine concentration in spot urine samples obtained during pregnancy and for 52 weeks postpartum in women receiving iodine supplementation and control women. The last sample was obtained after iodine supplementation was stopped.

groups. In contrast, serum Tg was lowered to nearly half of the control values by iodine supplementation of the mother.

TPO antibodies were found in the serum of four women at the initial visit (two in the control group and two in the iodine-supplemented group). Detectable amounts of antibodies were found during the entire study in all four women, with an increase in levels postpartum. In the two women from the control group, this was not associated with abnor-

TABLE 2. Iodine in breast milk and urine from the newborns on day 5 after delivery

	Iodine-supplemented	Controls	P
Iodine in breast milk ($\mu\text{g/L}$)	41 (31-74)	28 (19-46)	0.06
Iodine in urine from the child ($\mu\text{g/L}$)	64 (34-70)	27 (21-56)	0.01

Milk samples were obtained from 27 mothers in the iodine-supplemented group and 26 in the control group. Urinary samples were obtained from 27 and 25 children. P values indicate the level of statistically significant difference between groups. Values are medians (95% confidence intervals).

TABLE 3. Measurements in cord blood

	Iodine-supplemented	Controls	P
TSH (mU/L)	6.8 (4.9-8.1)	7.8 (4.8-11.9)	NS
Tg ($\mu\text{g/L}$)	38 (18-49)	67 (35-85)	0.005
Free T_4 (pmol/L)	13.6 (12.6-15.2)	13.6 (12.8-14.2)	NS
T_4 (nmol/L)	164 (140-187)	165 (143-176)	NS
T_3 (nmol/L)	0.70 (0.60-0.86)	0.74 (0.65-0.82)	NS

Data [median (95% confidence interval)] for serum from cord blood. The women were randomized to the presence or absence of iodine supplementation (200 $\mu\text{g/day}$).

malities in thyroid function. One of the two women receiving iodine supplementation developed high serum T_3 and T_4 and suppressed serum TSH levels 3 months after delivery and had persistent biochemical signs of hyperthyroidism at 6, 9, and 12 months. The other woman developed slightly increased serum TSH (9-10 mU/L) 9 and 12 months postpartum, with serum T_4 and T_3 levels in the normal range. The values from these two women have been included for calculations, but nearly identical results were obtained if they were excluded.

Discussion

The relationship between pregnancy and thyroid function has been discussed in detail recently (11, 19, 28, 29), and alterations in the various hormones in serum, as seen in our area, are well described (21). The object of the present study was to evaluate to which degree the variations observed in previous studies could be due to a relative iodine deficiency pre- and postpartum. Such information is pertinent to the question of the necessity of iodine supplementation during and after pregnancy in areas with moderately low iodine intake but no endemic goiter or cretinism.

The women studied lived in an area of Denmark where iodine intake is relatively low. The urinary iodine values observed in the present study were similar to the values observed in a previous study (14) and correspond to values found in this area nearly 30 yr ago (4). The women were selected so that none took iodine-containing vitamin/mineral tablets. In an independent study we found that approximately one third of Danish women take such tablets during pregnancy (8). Only minor variations in urinary iodine concentrations were observed during pregnancy in the control group. In the first sample after delivery, the values were

approximately 30% lower. The mechanism behind this fall is unknown. One possibility is that it is caused by the acceleration in lactation with accumulation of iodine in mammary glands. From an epidemiological point of view, it is important to know that urinary samples collected shortly after delivery may give relatively low iodine values.

In our pilot study of pregnant women in this area, we observed a high serum Tg level in late pregnancy (14). Similar high levels were found by some researchers (30, 31), whereas low values were observed in other studies (32). This difference is probably due to a difference in iodine intake levels. In the present study a considerable increase in serum Tg during pregnancy was observed in the control group, and this was abolished by iodine supplementation.

In a previous longitudinal study of normal pregnant women performed in our area, serum TSH showed a small, but significant, increase during pregnancy (21), and such a variation was also observed in the control group in the present study. It seems that this was also caused by a relative iodine deficiency in the mother. The TSH increase was not observed during iodine supplementation.

One of the consequences of the pregnancy-associated increase in demand on the thyroid is an increase in thyroid volume. This is well known by clinicians and has been demonstrated by several investigators using sonographical measurements of thyroid volume (17–19). Possibly, a relative increase in mild to moderate iodine deficiency during pregnancy could also be involved in this variation. This was supported by the finding of Crooks *et al.* (33) of a much higher pregnancy-associated prevalence of goiter in a low iodine intake area compared to that in a high iodine intake area. The results of the present study suggest that a relative iodine deficiency during pregnancy may be the cause of some, but not all, of the increase in thyroid volume. Notably, the size of the thyroid returned to initial values after delivery independent of iodine supplementation. Recently, Romano *et al.* (34) found a similar amelioration of the pregnancy-associated increase in thyroid size by iodine supplementation.

Iodine supplementation did not induce significant alterations in serum T₄, T₃, or free T₄ during pregnancy and the first year postpartum. The thyroid function of the child was evaluated by analyses of cord blood. A large difference was observed in the concentrations of Tg in the two groups, but no difference was found in T₄, T₃, free T₄, or TSH.

So, clearly, iodine supplementation had an effect on both the fetal and maternal thyroid. Serum Tg was much lower during iodine supplementation, and the increase in size of the maternal thyroid during pregnancy was considerably less when iodine was taken. Apparently, the thyroid gland had been able to adapt to the state of iodine deficiency in both the fetus and mother. Apart from TSH variations in the normal range in the mother, no difference in thyroid function, as evaluated by serum T₄, T₃, free T₄, and TSH, was observed in mother or child.

What, then, are the consequences of low iodine intake, and should an increase in iodine intake be recommended? A normal level of thyroid hormones is important for normal

development of the brain (12). In the present study we found no evidence of abnormalities in thyroid hormone levels in the newborn. Even serum TSH, which is a very sensitive marker of lack of thyroid hormone, was not altered by iodine supplementation. The adaptive capacity of the fetus to protect against lack of thyroid hormone is considerable (35), and it is difficult to imagine that the children born to control mothers in the present study have been at risk of developmental disorders due to iodine deficiency. On the other hand, the consequences of a lack of thyroid hormones can be severe, and it is important to ensure a considerable safety margin. The participants in the present study were absolutely normal, and the groups studied were relatively small. Possibly, a small part of the population, such as preterm infants (13), could be at a higher risk.

The other concern is the possible effect on the thyroid glands of mother and child. The increase in maternal thyroid volume and serum and cord blood Tg levels in the control group compared to those in the iodine-supplemented group indicate thyroidal stress by iodine deficiency. Such stress leads to goiter, which is primarily reversible, as was the increase in thyroid volume observed in the present study. However, at some point iodine deficiency triggers, by an unknown mechanism, irreversible changes in the thyroid with autonomous growth and function (36). In Denmark, such changes lead to a high incidence of multinodular toxic goiter in elderly subjects (10). It is not known when in life the primary events occur, and how long and severe the periods of iodine deficiency have to be. It is possible that relative iodine deficiency during pregnancy or even during fetal life could be a factor of importance for the late development of thyroid autonomy.

Probably, there will be no side-effects of increasing iodine intake during pregnancy. During the postpartum period, the two women with circulating TPO antibodies who received iodine both developed abnormalities in thyroid function, whereas no such alterations were observed in the two women from the control group. The groups were too small to draw any conclusion from this observation. However, we have previously obtained results suggesting that a high iodine intake is correlated with a considerably higher incidence of Graves' disease in young subjects (10). Further, Kämpe *et al.* (37) studied the effect of T₄ or iodine supplementation during weeks 1–40 after delivery to women with TPO antibodies. Iodine supplementation appeared to enhance thyroid dysfunction in some women. This was statistically significant compared to the control group. More studies on this phenomenon are necessary, but it seems inappropriate at present to give iodine supplementation postpartum to women with known autoimmune thyroid disease.

In Denmark, nearly all pregnant women take some type of vitamin/mineral tablet (8). Some of these tablets contain iodine, normally 150 µg/tablet. An easy way to increase iodine intake during pregnancy in Denmark would be to advocate that iodine-containing tablets should be chosen regularly. Even if the risk of relative iodine deficiency during pregnancy appears limited, it may be reasonable to suggest such a strategy for our area. In other areas with a similar low

iodine intake, the strategy may have to be different, depending on local habits. At present, we do not advocate regular iodine supplementation during the postpartum period.

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