

Earliest prevention of endemic goiter by iodine supplementation during pregnancy*

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During pregnancy complex changes of maternal thyroid function occur and they are influenced by the maternal iodine supply. It has been demonstrated that with decreasing iodine supply maternal goiter and hypothyroxinemia as well as fetal and neonatal hypothyroidism become more prevalent. Therefore iodine supplementation during pregnancy is now strongly recommended also in areas of moderate iodine deficiency. To monitor the success of iodine supplementation and its theoretical risk of increasing the frequency of thyroid autoantibodies, we have investigated the thyroid volume, thyroid function, urinary iodine excretion and antibodies to thyroid peroxidase at 10–12 weeks of gestation and postpartum in 38 mothers receiving 300 µg potassium iodide/day and in 70 mothers without iodine supplementation. In all of their newborns thyroid volume was determined by ultrasound. The thyrotropin (TSH) levels and antibodies to thyroid peroxidase (TPO-ab) in the neonates were measured in dried blood spots on filter paper from their newborn screening. Urinary iodine excretion was increased significantly after iodine supplementation in mothers ($p < 0.001$) and their newborns (< 0.05). No hypo- or hyperthyroidism was observed in the mothers or newborns. Interestingly, no difference of maternal thyroid volumes was observed between the two groups after pregnancy, but the volumes of the thyroid glands in newborns of mothers who received iodine were significantly ($p < 0.004$) lower (0.7 ± 0.4 ml) than in the control group (1.5 ± 1.1 ml). There was no change in the frequency of TPO-ab in either group after pregnancy. In four mothers transplacental passage of these antibodies was documented by positive measurement in the blood sample of the newborn. This study documents that iodine supplementation during pregnancy in an area of moderate iodine deficiency results in a lower size of neonatal thyroid volume and that this supplementation was not accompanied by an increase in the frequency of TPO-ab.

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Maternal and fetal thyroid function during pregnancy, although independently regulated, deteriorate with an increasing degree of iodine deficiency. Severe iodine deficiency throughout pregnancy can result in neonatal goiter and hypothyroidism with the long-term consequence of mental retardation and neurological sequelae (1–3). Also, in areas of moderate iodine deficiency the consequences on maternal and fetal thyroid function have been described recently (4–6), demonstrating a high frequency of maternal hypothyroxinemia, a high frequency of maternal and fetal goiter and an increase of neonatal hyperthyrotropinemia (7). Because it has been shown that in contrary to previous results there is a placental transfer of thyroxine in the human (9), iodine supplementation during pregnancy is now strongly recommended. Because of the results of some experimental (10–12) and epidemiological studies

(13–17) showing that iodine supplementation might be accompanied by an increase of thyroid autoantibodies the straightforward acceptance of this recommendation was delayed. Therefore a prospective randomized trial of iodine supplementation was conducted to study the effects on maternal and fetal thyroid volume, thyroid function and frequency of antibodies to thyroid peroxidase (TPO-ab).

Subjects

One hundred and eight pregnant women with a mean age of 32.4 years (21–40 years) consulting the Pregnancy Care Unit of the Benjamin Franklin Hospital of the Free University Berlin participated in the study. None had clinical evidence of autoimmune thyroid disease (ATD), 14 had a history of goiter and in seven a goiter was evident at first presentation.

*On the occasion of the 65th birthday of Professor Hans Helge.

Study design

The women were randomly assigned to two groups, according to the two different days of the week when they presented first in the Pregnancy Care Unit (Monday: iodine supplementation with 300 µg of potassium iodine throughout pregnancy and lactation; Tuesday: control group without iodine supplementation). At the beginning of pregnancy (mean: 11.2 weeks of gestation) and postpartum (mean: 11 days, 2–21 days), blood and urinary samples were collected from the mothers and thyroid volume was estimated. In the newborns the blood spots and the urine samples of the 5th day of life that were left after the routine neonatal screening were used for the laboratory investigations and the thyroid volume was measured by ultrasound.

All women gave informed consent for participating in the study, which was performed in agreement with the recommendations of the Ethical Committee of the Free University Berlin.

Methods

Hormone determination

Total thyroxine (TT₄), total triiodothyronine (TT₃) and thyrotropin (TSH) were measured by immunofluorimetric assays (DELFA), and thyroglobulin (TG) and thyroxine-binding globulin (TBG) were assayed by radioimmunoassay.

Urinary iodine

Urinary iodine and creatinine excretion were measured in a random urine sample in duplicate by the Ce/As method as described by Sandell and Kolthoff (18). Creatinine was measured by the standard technique described by Jaffe (19). The values of urinary iodine excretion were given as µg/dl or as the calculated ratio of iodine and creatinine (1 µg/g creatinine). Internationally, both methods of expressing values are used.

The compliance of potassium iodide intake as tablets was good, according to interviewing the mothers; however, regarding the lower iodine excretion in seven mothers, a poor compliance cannot be excluded in these individuals.

Antibodies to thyroid peroxidase

Thyroid peroxidase antibodies were analyzed by radioimmunoassay (DYNOTest[®] anti-TPO, Henning). Levels >300 U/ml were considered as clearly positive. To avoid additional blood sampling in the newborns, TPO-ab were determined in dried filter-paper blood spots of the 5th day of life that were left over from routine screening. We have published previously a high correlation ($r = 0.73$) between serum samples and filter-paper specimens (20).

Thyroid volume

Thyroid volume was measured by ultrasound using a 5.0-MHz linear transducer (Picker 2300) in the mothers and a 7.5-MHz sector scanner (Siemens Sonoline) in the newborns. Determinations were carried out by a single experienced investigator who was not aware to which group the proband belonged. Thyroid volume was quantified according to Brunn (21) using the following equation:

$$\text{Thyroid volume (ml)} = \text{Length (mm)} \times \text{Width (mm)} \\ \times \text{Thickness (mm)} \times 0.479$$

Thyroid volumes >18 ml in the mothers are regarded as enlarged according to the reference data established by Gutekunst (22) in Germany as a moderate iodine-deficient country. A neonatal thyroid gland volume >1.5 ml was defined as enlarged based on the findings of Chanoine (23), Einkenkel (24) and Klingmüller (25).

Statistical analysis

Statistical analysis was carried out using SPSS 5.0 (Statistical Package for Social Science). Data with a skewed distribution are expressed as medians and ranges. Spearman rank correlation tests were performed to study any relation and the Mann–Whitney U-test was performed for non-paired group differences and the Wilcoxon test for paired differences within groups; $p < 0.05$ was considered as statistically significant.

Results

At the beginning of gestation the median urinary iodine concentration was 53.2 µg/g creatinine or 6.4 µg/dl, with no statistically significant difference between mothers subsequently receiving 300 µg KI/day (49.2 µg/g creatinine) and the controls (54.9 µg/g creatinine). At the end of pregnancy iodine excretion was significantly ($p < 0.001$) increased to 104.5 µg/g creatinine in the group with potassium iodide supplementation compared to the controls. In the newborns, iodine excretion was also significantly higher ($p < 0.05$) after maternal supplementation with 8.3 µg/dl iodine vs 6.5 µg/dl in the newborns of the control group. There was no significant correlation between the thyroid volumes and the iodine excretion in the mothers or newborns (Fig. 1).

Iodine supplementation did not change thyroid function, as reflected by TSH, T₄ and T₄/TBG ratios; however, in the mothers of both groups low thyroxine levels were observed already 2 weeks after pregnancy, probably reflecting a significant degree of iodine deficiency, because iodine excretion even in the treated mothers was not corrected to normality in nine. In none of the mothers was hypo- or hyperthyroidism observed (Table 1).

Thyroid volume of the mothers at the beginning of

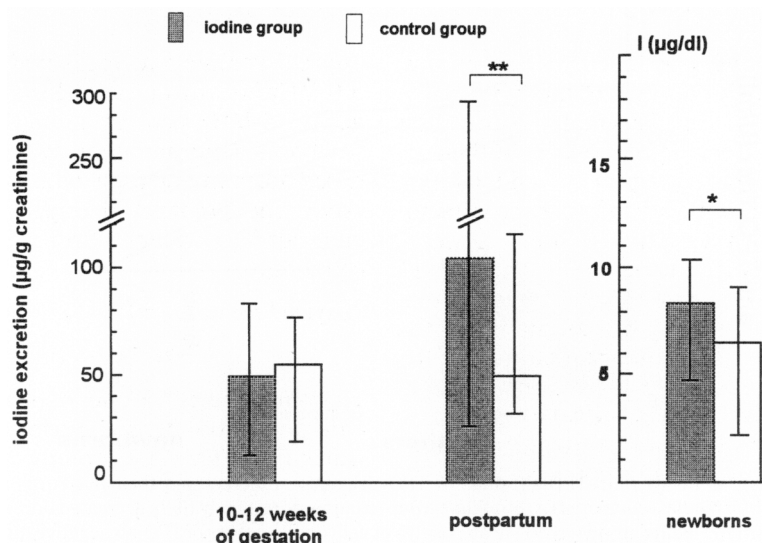


Fig. 1. Maternal urinary iodine concentration ($\mu\text{g/g}$ creatinine, median, 25/75 percentile) at 10–12 weeks of gestation and postpartum and neonatal urinary iodine concentration ($\mu\text{g/dl}$, median, 25/75 percentile) in the iodine group (hatched bars) compared to the control group (** $p < 0.001$, * $p < 0.05$).

gestation did not differ between either group (16.2 ml vs 16.8 ml), with 46 mothers (42.5%) having a goiter with enlarged volumes >18 ml according to the normal ranges in the german population. However, the percentage of goiter would have been even higher if reference data from iodine sufficient areas had been used (26, 27). Astonishingly, the daily administration of $300 \mu\text{g}$ of potassium iodide did not prevent an increase of the maternal thyroid gland volumes during pregnancy. Despite iodine supplementation, thyroid

volume increased above 18 ml in 23 women (60%), and in 19 of them thyroid volume increased by more than 2 ml. In the control group at the beginning of pregnancy 29 (41%) had an enlarged gland above 18 ml and at the end of pregnancy this number had increased to 42 (60%).

In contrast a significant effect of iodine supplementation was observed in the newborns, with a significantly decreased median thyroid gland volume of 0.7 ml vs 1.5 ml after maternal iodine intake ($p < 0.004$) (Fig. 2).

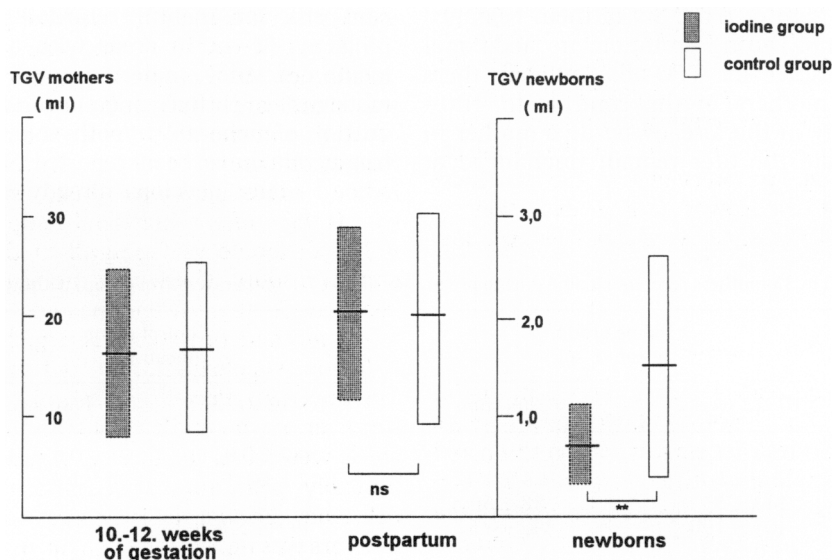


Fig. 2. Maternal thyroid gland volume (TGV, mean \pm SD) at beginning and end of gestation in the iodine group (dark bars) and in the control group (hatched bars), and TGV of the newborns at the age of 2 weeks (ns = no significance, ** $p < 0.004$).

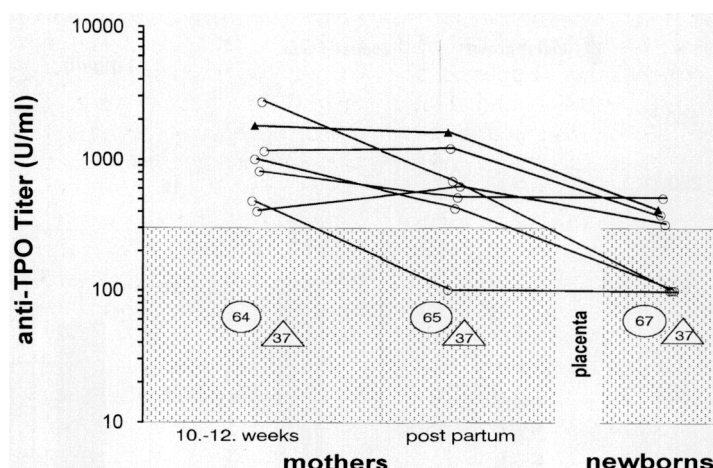


Fig. 3. Anti-thyroid peroxidase antibody (anti-TPO-ab) titers in TPO-ab positive mothers and their newborns at beginning of gestation and postpartum in the control group (circles) compared to the iodine group (triangles). Antibody titers decreased during pregnancy. Three newborns in the control group and one in the iodine group were TPO-ab positive at delivery. Numbers of TPO-ab negative mothers and newborns are given inside the circles and triangles. Normal range is the shaded area.

Considering a neonatal thyroid volume of >1.5 ml as goiter, according to the findings of other authors in Germany and Belgium (23–25), only one newborn in the supplementation group compared to 14 newborns of the controls had an enlarged thyroid gland. Although there was no correlation between individual maternal and neonatal thyroid volumes, a positive correlation was present between an increase of maternal thyroid volume of more than 2 ml and the thyroid size in the newborns of these mothers ($r = 0.73$, $p < 0.05$).

At the beginning of pregnancy seven mothers had positive TPO-ab measurements (370–2600 U/ml), without any other sign of ATD. Six of them belonged to the control group. During gestation, no additional mother became positive for TPO-ab. Antibody titers decreased in five mothers in the controls to 100–1750 U/ml and only in the already positive mother in the iodine group did the titer remain unchanged at 1600 U/ml.

Four of the newborns of these mothers were positive as well, including the one in the iodine group, but no other newborn had detectable TPO-ab (Fig. 3). Therefore, no enhancement of placental transfer or induction of autoimmunity was observed as a consequence of iodine supplementation.

Discussion

Severe maternal iodine deficiency during pregnancy creates a risk for abnormal development of the fetal central nervous system. Furthermore, when accompanied by maternal hypothyroxinemia there is a significant risk for mental retardation and neurological problems (2–4). In areas with a moderate degree of iodine deficiency, maternal and fetal goiter formation, maternal hypothyroxinemia and an increased frequency of neonatal hypothyroidism and hyperthyrotropinemia have been reported (7, 8). Because every second goiter develops already during the first two

Table 1. Thyroid function in 38 mothers receiving iodine during pregnancy and in 70 mothers (control group) without iodine supplementation.^a

	Iodine group (mean \pm SD)		Control group (mean \pm SD)		Normal
	10–12 weeks	Postpartum	10–12 weeks	Postpartum	
TSH (mU/l)	0.84 \pm 1.1	0.57 \pm 0.8	0.7 \pm 0.9	0.9 \pm 1.2	0.3–4.0
T ₃ (nmol/l)	2.1 \pm 1.1	1.4 \pm 1.1	2.1 \pm 1.1	1.5 \pm 1.4	1.1–3.1
T ₄	113 \pm 55	88 \pm 60	113 \pm 62	68 \pm 61	50–160
TGB (mg/dl)	405 \pm 190	342 \pm 252	399 \pm 228	313 \pm 277	220–510
T ₄ /TGB	4.0 \pm 0.1	3.1 \pm 0.2	3.8 \pm 0.1	2.3 \pm 0.7	2.6–7
TG (μ g/l)	16.5 \pm 18.5	8.3 \pm 10.9	16.6 \pm 19.2	13.5 \pm 19.3	< 50

^a No statistically significant differences were observed. TBG = thyroxine-binding globulin.

decades of life (28), earliest prevention of goiter formation is a pediatric task of high medical and socioeconomic priority. Therefore, iodine supplementation has to start already during gestation and it has been shown that this will result in the disappearance of visible goiter in newborns in areas of severe iodine deficiency (29–31). In areas of moderate iodine deficiency a few studies have addressed the influence of maternal iodine intake during pregnancy on neonatal thyroid volume by measuring the neonatal thyroid volume by ultrasound (32), and only one study investigated the development of thyroid antibodies during iodine supplementation in pregnancy (33). This is, to our knowledge, the first randomized trial investigating both the effect on the neonatal thyroid size and the theoretical risk of antibody formation.

In this trial, iodine supplementation reduced the size of the thyroid gland of the newborns to the same extent as has been published recently by Glinioer et al. (32), but in contrast to their findings and to other studies (34) iodine supplementation could not prevent the increase of the maternal thyroid volumes. Several reasons for the failure to normalize maternal thyroid volume during pregnancy in the present study can be considered, including the relatively high age of the mothers (32 years) with therefore already fixed goiter formation or a still insufficient iodine dose, because iodine excretion was only borderline in seven mothers of the iodine group and the urinary iodine excretion rose only by about 50 µg/g creatinine. The small increase may also be due to the loss of maternal iodine to the fetal–placental unit and to an increased renal clearance during pregnancy (35). More general explanations for the difficulty in normalizing maternal thyroid volumes during pregnancy are the influences of other factors stimulating thyroid growth, such as human chorionic gonadotropin (hCG), epidermal growth factor (EGF) and insulin-like growth factor I (IGF-I), which also have to be taken into account (36–38).

Although no significant changes of thyroid function have been observed, it is interesting that maternal TT₄ levels have decreased rapidly after birth to low–normal levels, most likely reflecting the significant degree of iodine deficiency in the studied area.

The data on serum thyroglobulin levels in pregnancy are in contrast to the findings of other authors (33, 39, 40). In this study a more pronounced decrease of thyroglobulin serum levels, though statistically not significant, was present in the group of mothers receiving iodine supplementation, but overall there was no correlation to the thyroid volumes. This again may be explained by other factors influencing the thyroid size during pregnancy, such as increased water content and vascularization of the gland.

There are several epidemiological studies that describe an increase of thyroid autoimmune disease after the introduction of iodine supplementation (14–16). For iodine supplementation during pregnancy

there are only scarce data on antibody formation during gestation, but a recent study (41) described an increase in postpartum thyroiditis after iodine supplementation during pregnancy. Furthermore, ATD during pregnancy carries the risk of transplacental passage of maternal antithyroid immunoglobulins, resulting in hypothyroidism (42–45) or hyperthyroidism (46) of the newborn. In this study no mother developed autoantibodies during pregnancy and those mothers having already positive TPO-ab at the beginning of gestation showed no increase of the antibody titers.

Therefore, it may be concluded from this study that the administration of 300 µg KI/day during pregnancy in an area of moderate iodine deficiency prevents the development of fetal thyroid enlargement without increasing the risk of maternal autoimmunity.

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