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CLINICAL STUDY

Iron supplementation in goitrous, iron-deficient children improves their response to oral iodized oil

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Abstract

Objective: In developing countries, many children are at high risk for both goiter and iron-deficiency anemia. Because iron deficiency may impair thyroid metabolism, the aim of this study was to determine if iron supplementation improves the response to oral iodine in goitrous, iron-deficient anemic children.

Design: A trial of oral iodized oil followed by oral iron supplementation in an area of endemic goiter in the western Ivory Coast.

Methods: Goitrous, iodine-deficient children (aged 6–12 years; $n = 109$) were divided into two groups: Group 1 consisted of goitrous children who were not anemic; Group 2 consisted of goitrous children who were iron-deficient anemic. Both groups were given 200 mg oral iodine as iodized oil. Thyroid gland volume using ultrasound, urinary iodine concentration (UI), serum thyroxine (T_4) and whole blood TSH were measured at baseline, and at 1, 5, 10, 15 and 30 weeks post intervention. Beginning at 30 weeks, the anemic group was given 60 mg oral iron as ferrous sulfate four times/week for 12 weeks. At 50 and 65 weeks after oral iodine (8 and 23 weeks after completing iron supplementation), UI, TSH, T_4 and thyroid volume were remeasured.

Results: The prevalence of goiter at 30 weeks after oral iodine in Groups 1 and 2 was 12% and 64% respectively. Mean percent change in thyroid volume compared with baseline at 30 weeks in Groups 1 and 2 was −45.1% and −21.8% respectively ($P < 0.001$ between groups). After iron supplementation in Group 2, there was a further decrease in mean thyroid volume from baseline in the anemic children (−34.8% and −38.4% at 50 and 65 weeks) and goiter prevalence fell to 31% and 20% at 50 and 65 weeks.

Conclusion: Iron supplementation may improve the efficacy of oral iodized oil in goitrous children with iron-deficiency anemia.

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Introduction

Iodine deficiency produces a spectrum of disorders – endemic goiter, hypothyroidism, cretinism and congenital anomalies – that are termed the iodine-deficiency disorders (IDD) (1). In western and central Africa, it is estimated that 250 million people are at risk for IDD and 50 million have goiter (2). In iodine-deficient areas, multiple nutritional and environmental influences contribute to the prevalence and severity of IDD (3). Goitrogenic foods and water-borne goitrogens can aggravate goiter (4, 5). General malnutrition and deficiencies of selenium (6, 7) and vitamin A (8) may modify thyroid hormone metabolism and potentially exacerbate IDD.

Another micronutrient that can potentially influence IDD is iron (9, 10). The two initial steps of thyroid hormone synthesis are catalyzed by thyroperoxidases and are dependent on iron. Animal and human studies have suggested iron deficiency impairs thyroid metabolism. Iron-deficiency anemia decreases plasma thyroxine (T_4) and triiodothyronine (T_3) levels, reduces peripheral conversion of T_4 to T_3 and may increase circulating thyroid-stimulating hormone (TSH) (11–14).

Deficiencies of iron and iodine are major public health problems in the developing world, where many children are at high risk for both goiter and iron-deficiency anemia (15). In the western Ivory Coast, 30–50% of schoolage children are goitrous and 23–25% suffer from iron-deficiency anemia (16, 17). We have recently shown that concurrent iron-deficiency anemia impairs the response of iodine-deficient, goitrous children

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to oral iodized oil (9). The aim of the present study was to determine if iron supplementation improves the response to oral iodine in goitrous, iron-deficient anemic children.

Subjects and methods

The study was carried out in two isolated villages (total population, 1450) in an area of endemic goiter in the Danané Health District (16, 17), a mountainous region in the western Ivory Coast. The median urinary iodine concentration (UI) (95% confidence interval (CI)) in schoolage children in this area is 28 (28–46) μg/l (9), indicating moderate-severe iodine deficiency (1). The study was approved by the Ethical Review Board of the University Hospital of Zurich, the National Institute of Public Health and the Ministry of Research of the Ivory Coast. Informed consent was obtained from the village chiefs and the families of the individual children.

All children aged 6 to 15 years in the two villages ($n = 419$) were screened for goiter and iron-deficiency anemia. The results of this screening have been described previously (9). All goitrous 6- to 12-year-old children who met the following criteria were then invited to join the intervention study: Group 1 consisted of goitrous children with a hemoglobin (Hb) >120 g/l; Group 2 consisted of goitrous children with iron-deficiency anemia. Iron-deficiency anemia was considered present if: Hb <110 g/l and serum ferritin <12 μg/l; or Hb <110 g/l and transferrin receptor (TfR) >8.5 mg/l and zinc protoporphyrin (ZPP) >40 μmol/mol heme (18). Fifty-eight children met the criteria for Group 1 and 53 were enrolled, while 71 children met the criteria for Group 2 and 56 were enrolled. Throughout the entire study the investigators were blind to the group assignment of the children.

Baseline measurements on all children just before administration of the iodized oil included iodine concentration in spot urine samples (UI) and whole blood TSH and serum T_4 from blood spotted onto filter paper. Thyroid gland volume was measured using an Aloka SSD-500 Echocamera (Aloka, Mure, Japan) with a high-resolution 7.5 MHz linear transducer (19).

Each child in Groups 1 and 2 then received an oral dose of 0.4 ml iodized poppyseed oil (Lipiodol; Guerbet, Roissy CdG Cedex, France) containing 200 mg iodine. At 1, 5, 10, 15 and 30 weeks post intervention, spot urines were collected for measurement of UI and dried blood spots for determination of TSH and T_4. At 10, 15 and 30 weeks, thyroid volume was measured using ultrasound. At 10, 15 and 30 weeks, height and weight were remeasured to account for the potential effect of growth on thyroid volume. At 30 weeks a venous blood sample was collected for measurement of Hb. Of the 109 children who began the study, 104 completed it to 30 weeks. Of the five children who did not complete the study, one child from Group 1 and two from Group 2 could not be traced. One child from Group 1 developed anemia during the study and one child in Group 2 was no longer anemic at 30 weeks; they were both excluded.

Beginning at 30 weeks, each child in Group 2 received 60 mg oral iron as ferrous sulfate four times/week for 12 weeks. Hb, UI, TSH, T_4 and thyroid volume were measured at 50 weeks (8 weeks after completion of iron supplementation) in all children. At 65 weeks, UI, TSH, T_4 and thyroid volume were measured in all children in Group 2 and in a sample of 15 children from Group 1.

In countries with a high prevalence of child growth retardation, thyroid volume is considered to be more directly a function of total body surface area (BSA) than of age (20). Therefore, BSA was calculated from weight and height measurements taken with each ultrasound measurement, and normative values for thyroid volume in children aged 6–12 years according to sex, age and BSA were used to define the presence or absence of goiter (20). To avoid interobserver variability, all ultrasound measurements were performed by a single investigator (MZ). Calculated from a set of eight repeated determinations in six children at baseline (mean thyroid volume = 8.3 ml), the variability of the thyroid volume measurement using ultrasound was small (range of S.D. = 0.12–0.14 ml).

Biochemical analyses

Blood and urine samples were aliquoted and frozen at −20 °C until analysis. UI was measured using a modification of the Sandell–Kolthoff reaction (21). Hb was measured using the cyanmethemoglobin method with kits (Sigma Diagnostics, St Louis, MO, USA) and three-level quality control materials (DiaMed, Cressier sur Morat, Switzerland). Because normal values for Hb may be lower in black individuals, to ensure the iron-deficient children in this study were anemic, a WHO-1 cut-off was used for anemia (22). ZPP was measured on washed red blood cells using a hematofluorimeter (Aviv Biomedical, Lakewood, NJ, USA). Serum ferritin and TfR were measured using commercial kits (RAMCO, Houston, TX, USA). Dried blood spots on filter paper were analyzed for whole blood TSH and serum T_4 using immunoassay (23). Normal reference values are: UI, 50–250 μg/l; serum ferritin, 12–300 μg/l; TfR, 2.9–8.5 mg/l; ZPP, <40 μmol/mol heme; whole blood TSH, <3.5 mU/l; serum T_4, 65–165 nmol/l.

Statistics

Data which were normally distributed were expressed as means (S.D.) and were compared by Student's *t*-test. Parameters not normally distributed (UI, TSH) were expressed as medians with 95% confidence intervals (CIs), and were compared by Wilcoxon and Mann–Whitney tests. A two-factor repeated measures ANOVA was done to compare effects of time and group and time

Table 1 Baseline characteristics of children in Groups 1 and 2. Data which were normally distributed are expressed as means (S.D.) and compared by Student's *t*-test. Parameters not normally distributed (UI, TSH) are expressed as medians (95% CI) and compared by Wilcoxon and Mann–Whitney tests.

Characteristic	Group 1 (goitrous and nonanemic) ($n = 51$)	Group 2 (goitrous and iron-deficiency anemia) ($n = 53$)
Age (years)	8.6 (1.9)	8.2 (1.9)
Sex (F/M)	23 F, 28 M	26 F, 27 M
Weight (kg)	25.9 (6.2)	23.1 (6.4)*
Height (cm)	128 (13)	120 (14)*
BMI (kg/m^2)	15.8 (1.5)	15.9 (1.7)
Hemoglobin (g/l)	125 (4)	97 (8)
Serum ferritin (μg/l)	77.2 (31)	16.1 (5.9)
Serum TfR (mg/l)	6.6 (4.1)	122.6 (31.4)
Whole blood ZPP (μmol/mol heme)	23 (12)	71 (26)
Median UI (μg/l)	29 (30–47)	27 (28–46)
Whole blood TSH (mU/l)	1.1 (1.1–1.3)	0.8 (0.8–1.4)
Serum T_4 (nmol/l)	110 (22)	130 (28)*
Thyroid volume (ml)	8.5 (2.0)	8.1 (1.9)

* $P < 0.05$ between groups.

by group for UI, TSH, T_4 and percent change in thyroid volume after intervention.

Results

Table 1 compares Groups 1 and 2 at baseline. There were no significant differences in age or gender. Although the body mass indices (BMIs) of the groups were not different, the means for height and weight in Group 2 were significantly less ($P < 0.05$) than in Group 1. Overall, the children in Group 2 were moderately iron-deficient anemic (mean Hb 97 g/l), with 20% of the children having Hb <90 g/l. The mean serum total T_4 was significantly higher in Group 2 than in Group 1 ($P < 0.01$), although both means were well within the normal range. There were no significant differences in thyroid volume, UI or whole blood TSH between the groups.

Table 2 shows the changes in thyroid volume in Groups 1 and 2 over the course of the study. Thyroid volume decreased significantly vs baseline in both groups at 10 weeks ($P < 0.001$). At 15 and 30 weeks there were no further decreases in Group 2, while in Group 1, thyroid size continued to fall. At 15 and 30 weeks, thyroid volume was significantly reduced in Group 1 compared with Group 2 ($P < 0.001$). At 30 weeks the mean percent change in thyroid volume from baseline was −45% in Group 1 and −22% in Group 2. A sharp difference in goiter prevalence was apparent at 15 and 30 weeks, when goiter rates were 62% and 64% in Group 2 but only 31% and 12% in Group 1 (Fig. 1).

Iron supplementation in Group 2 resulted in an increase in mean Hb (S.D.) from 97 (8) g/l at 30 weeks to 122 (8) g/l at 50 weeks. Only 6 of the 51 children in Group 2 remained anemic (Hb <110 g/l) at 50 weeks. Change in thyroid volume from baseline in Group 2, which had plateaued at weeks 10 to 30, began to fall again after iron supplementation, to a mean (S.D.) of −34.8 (14.2) and −38.4 (13.6) at 50 and 65 weeks respectively. Goiter prevalence in Group 1, which had remained at 62–64% from weeks 10 to 30, was reduced after iron supplementation to 31% and 20% at 50 and 65 weeks (Fig. 1).

Table 3 shows the changes in TSH, T_4 and UI in Groups 1 and 2 over the 65 weeks of follow-up. UI remained significantly increased above baseline

Table 2 Changes in thyroid volume (ml) (mean (S.D.)) in Group 1 (goitrous, nonanemic children) and Group 2 (goitrous, iron-deficient anemic children) over 65 weeks after receiving 200 mg oral iodine. From the 30th–42nd week, Group 2 received 60 mg oral iron as ferrous sulfate 4 ×/week.

	Group 1 ($n = 51$)	Group 2 ($n = 53$)
At baseline	8.5 (2.0)	8.1 (1.9)
At 10 weeks	6.5 (1.7)$^+$	6.5 (2.6)$^+$
Change (%) from baseline	−22.3 (17.3)	−20.0 (19.5)
At 15 weeks	5.1 (1.5)$^+$*	6.3 (2.4)$^+$
Change (%) from baseline	−30.7 (14.8)	−22.8 (18.8)
At 30 weeks	4.6 (1.5)$^+$*	6.3 (2.1)$^+$
Change (%) from baseline	−45.5 (12.0)	−21.8 (17.2)
At 50 weeks	4.3 (1.3)$^+$*	5.4 (1.7)$^+$
Change (%) from baseline	−46.9 (13.7)	−34.8 (14.2)
At 65 weeks**	4.5 (1.5)$^+$*†	5.0 (1.5)$^+$
Change (%) from baseline	−46.1 (12.9)	−38.4 (13.6)

Two-factor repeated measures ANOVA was performed to compare effects of time and group and time by group after intervention. $^+$ $P < 0.001$ vs baseline. † $P < 0.05$ between groups. * $P < 0.001$ between groups.

** Thyroid volume at 65 weeks was measured only on a subset of 15 children in Group 1. To reduce the effects of variability among individuals, percent change from baseline was calculated for each child before deriving means.

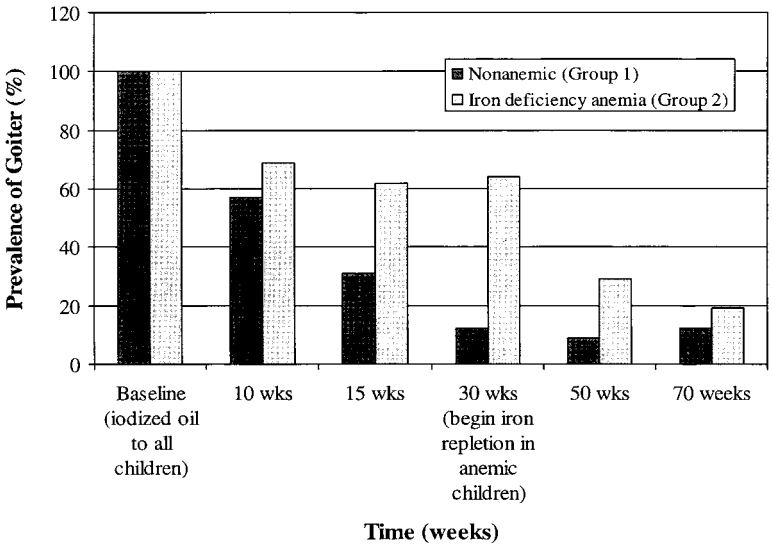

Figure 1 Number of subjects in Group 1 (goitrous, nonanemic children) and Group 2 (goitrous, iron-deficient anemic children) with goiter by ultrasound over 65 weeks after receiving 200 mg oral iodine.

throughout the 65 weeks in both groups ($P < 0.01$); the median UI (95% CI) in both groups was 96 (87–118) μg/l and 61 (44–86) μg/l at 50 and 65 weeks respectively. At baseline and at all follow-up points, median TSH and mean serum T_4 were within the normal range in both groups. In Group 2 at 1 week, there was no change in mean serum T_4 but a significant transient rise in the median TSH value, consistent with a mild Wolff–Chaikoff effect. Median TSH values at 5, 10, 15, 30 and 50 weeks were reduced significantly ($P < 0.01$) compared with baseline in Group 1. At 15 and 30 weeks, median TSH values were significantly lower in Group 1 compared with Group 2 ($P < 0.01$). Mean serum T_4 increased significantly from baseline in Group 1 at 30 weeks ($P < 0.01$), and at 15 and 30 weeks T_4 values in Group 1 were significantly greater than those in Group 2 ($P < 0.001$). These values suggest that, over the first 30 weeks after treatment with oral iodine, thyroid hormone status improved in Group 1 compared with Group 2.

Table 3 Changes in whole blood TSH, serum T_4 and UI in Group 1 (goitrous, nonanemic children) and Group 2 (goitrous, iron-deficient anemic children) over 65 weeks after receiving 200 mg oral iodine. Values for TSH and urinary iodine are medians (95% CI). Values for T_4 are means (S.D.).

	TSH (mU/l)		**T_4** (nmol/l)		**UI** (μg/l)	
Weeks after iodine	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Baseline	1.1 (1.1–1.4)	0.8 (0.8–1.4)	110 (22)	130 (28)*	29 (30–47)	27 (28–46)
1	1.1 (1.1–1.5)	2.1**$^{+}$ (2.0–2.5)	113 (22)	131 (27)*	992^{++} (919–1500)	1210^{++}* (1450–2490)
5	0.6^{++} (0.5–0.7)	0.7 (0.7–1.0)	115 (21)	100 (22)	281^{++} (262–358)	359^{++} (331–445)
10	0.6^{++} (0.5–0.8)	0.8 (0.7–1.0)	110 (26)	101 (25)$^{+}$	168^{++} (165–231)	176^{++} (172–266)
15	0.5^{++} (0.4–0.6)	0.8* (0.8–1.0)	122 (24)	96 (17)$^{+}$**	181^{++} (165–218)	176^{++} (172–266)
30	0.6^{++} (0.5–0.6)	1.0** (1.1–1.4)	156 (30)$^{+}$	123 (30)**	125^{++} (115–143)	143^{++} (128–180)
50	0.7^{+} (0.6–0.9)	0.9 (0.8–1.2)	134 (31)	131 (28)	94^{++} (87–115)	97^{++} (85–119)
65**	0.8 (0.7–1.2)	0.8 (0.7–1.3)	125 (27)	119 (23)	62^{+} (46–89)	59^{+} (43–87)

Two-factor repeated measures ANOVA was performed to compare effects of time and group and time by group for UI, TSH and T_4 after intervention.
** Thyroid volume at 65 weeks was measured only on a subset of 15 children in Group 1.
$^{+}$ $P < 0.01$ vs baseline. $^{++}$ $P < 0.001$ vs baseline. * $P < 0.01$ between groups. ** $P < 0.001$ between groups.

Discussion

Studies in animals and humans have shown that iron deficiency impairs thyroid metabolism. In rats, iron deficiency reduces plasma thyroid hormone levels, reduces activity of hepatic thyroxine-5-deiodinase, impairs peripheral conversion of T_4 to T_3, and blunts the TSH response to thyrotropin-releasing hormone (12, 24). Compared with healthy controls, iron-deficient adults have lower circulating T_4 and T_3 levels (11, 13, 14) and higher TSH concentrations (14). Although the mechanism for these effects is unclear, the initial steps of thyroid hormone synthesis – iodide incorporation into tyrosine residues of thyroglobulin and covalent bridging of the residues – are catalyzed by heme-containing thyroperoxidases. Other iron-containing enzymes (e.g. cytochrome oxidase, myeloperoxidase and succinate-ubiquinone oxidoreductase) are sensitive to iron deficiency (25, 26). Theoretically, severe iron deficiency could lower thyroperoxidase activity and interfere with thyroid hormone synthesis (10). However, previous reports examining an interaction between iron deficiency and goiter are limited to cross-sectional surveys. There was no correlation between iron status and goiter rate or thyroid hormone levels in a survey in Ethiopian children (8, 27). In a study in the Philippines, there were no significant differences in the prevalence of goiter among anemic and nonanemic children and adults (28).

In this study, iron deficiency in the anemic children was confirmed at baseline using multiple iron status indicators (ferritin, TfR, ZPP). At 30 and 50 weeks post intervention, Hb was remeasured in all subjects, but because of technical considerations in the field, we were unable to redetermine iron status. Persistent anemia (Hb <110g/l) in the subjects in Group 2 previously diagnosed with iron-deficiency anemia was assumed to be due to continuing iron deficiency. This was confirmed by the excellent response to 12 weeks of iron supplementation in Group 2 (a mean increase in Hb of >20 g/l).

During the trial, the diets of the children in the two groups were not controlled, so it is unknown if they received equivalent diets in terms of calories and protein. Also, we did not measure circulating proteins (such as albumin) to compare nutritional status in the two groups. To compare nutritional status, we measured and compared weights and heights between the two groups, using growth as an indirect indicator of nutritional status during childhood. The mean BMIs of the children in the two groups were not significantly different and were near the 50th percentile for black children from the USA (37). There were no visible signs of acute protein-energy malnutrition in the children. However, the children in Group 1 were significantly smaller than those in Group 2, consistent with the known adverse effects of iron deficiency on childhood growth.

Thyroid ultrasonography is a precise and objective method for measuring goiter size that has become feasible for field studies even in remote areas (1). It is particularly valuable for accurate detection of small goiters in children (29) and, as shown in this study, measuring response to iodine repletion in children. The durable and portable echocamera used in this study was carried into the field and, in an area without electricity, run off a small generator. Each assessment required only a few minutes per subject. The children in Group 1 showed a rapid and sustained response to oral iodine; at 30 weeks, mean (S.D.) percent decrease in thyroid volume from baseline was −45.5% (12.0) and only 12% of the children remained goitrous. This marked reduction in goiter prevalence is more pronounced than those described by most previous authors (30–35), but because of varying conditions in these studies (age of subjects, severity of iodine deficiency, geographic location, ultrasound vs palpation for goiter grading, follow-up intervals), it is difficult to compare results. In a study by Benmiloud *et al.* (30) in iodine-deficient Algerian children aged 6–11 years, an oral dose of 240 mg iodine as iodized oil maintained urinary excretion >50 μg/l for 9 months, but there was no significant decrease in mean thyroid volume with treatment. In a study of goitrous adults in Zaire, a 118 mg oral dose of iodine reduced thyroid size, as measured by a thyroid tracing method, by 36% at 3 months and 52% at 1 year (35). In the present study, a 200 mg oral dose of iodine maintained adequate iodine status for at least 1 year. UI remained significantly increased above baseline during the entire trial ($P < 0.001$); the median UI at 50 weeks in Groups 1 and 2 was still 94 and 97 μg/l respectively, close to the WHO cut-off value (100 μg/l) for IDD risk in a population (1).

Compared with Group 1, the children in Group 2 showed a blunted response to oral iodine, as evidenced by the plateau at 10, 15 and 30 weeks in mean percent change in thyroid size from baseline and goiter prevalence. Correction of iron deficiency in Group 2 appeared to improve the thyroid response to iodine repletion. At 50 and 65 weeks, while iodine supply to the thyroid was maintained at adequate levels by the prolonged release of iodine from the iodized oil, iron treatment was associated with a significant further decrease in thyroid volume and a substantial reduction in goiter prevalence. A limitation of the study design was the lack of a control group of anemic goitrous children not treated with iron. Therefore, it is not possible to exclude other potential causes for the reduction in thyroid size after iron supplementation. However, in support of the direct effect of iron on goiter reduction, the six children from Group 2 who remained anemic after the period of iron supplementation did not show a significant further reduction in thyroid volume at 50 and 65 weeks. Mean thyroid volume (S.D.) at 50 and 65 weeks in these six children was 6.1 (2.0) ml and 5.8 (2.1) ml.

Although iron supplementation in the anemic children was associated with an improved response to iodized oil, there remained a significant difference in thyroid volume (and percent change from baseline) between the groups, even after iron repletion. At 50 and 65 weeks, thyroid volumes were significantly greater in Group 2 than in Group 1. This remaining difference could have resulted from several factors. Iron was given 30 weeks after the iodine, and a greater effect may have been seen if iron had been given at the beginning of the study, along with the iodine. Also, follow-up of the children after iron supplementation was for approximately 20 weeks, and the iron-supplemented children may have shown a further reduction in thyroid volume if follow-up had been for a longer period.

The findings in this study suggest that iron supplementation improves the efficacy of oral iodized oil in goitrous children with iron-deficiency anemia. More than 2 billion people – mainly young women and children, mostly in the developing countries – are iron deficient (36). Children are also highly vulnerable to iodine deficiency, and are one of the main target groups for iodine supplementation programs (1). In the western Ivory Coast, nearly one in five children suffers from both goiter and iron-deficiency anemia (9). If iron deficiency is a nutritional factor that influences the pathogenesis of IDD, it may have a greater impact on IDD than previously described goitrogens because of its high prevalence in vulnerable groups. It also argues strongly for the double fortification of salt with iodine and iron, not only to reduce the prevalence of iron deficiency, but also to potentially increase the efficacy of iodine in populations that are both iron deficient and goitrous.

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