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The Adverse Effects of Mild-to-Moderate Iodine Deficiency during Pregnancy and Childhood: A Review

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Iodine is required for the production of thyroid hormones, which are essential for normal brain development, and the fetus, newborn, and young child are particularly vulnerable to iodine deficiency. The iodine requirement increases during pregnancy and recommended intakes are in the range of 220–250 μg/day. Monitoring iodine status during pregnancy is a challenge. New recommendations from World Health Organization suggest that a median urinary iodine concentration between 150 and 250 mcg/L indicates adequate iodine intake in pregnancy. Based on this range, it appears that many pregnant women in Western Europe have inadequate intakes. A recent Swiss study has suggested that thyroid-stimulating hormone concentration in the newborn is a sensitive indicator of mild iodine deficiency in late pregnancy. The potential adverse effects of mild iodine deficiency during pregnancy are uncertain. Controlled trials of iodine supplementation in mildly iodine-deficient pregnant women suggest beneficial effects on maternal and newborn serum thyroglobulin and thyroid volume, but no effects on maternal and newborn total or free thyroid hormone concentrations. There are no long-term data on the effect of iodine supplementation on birth outcomes or infant development. New data from well-controlled studies indicate that iodine repletion in moderately iodine-deficient school-age children has clear benefits: it improves cognitive and motor function; it also increases concentrations of insulin-like growth factor 1 and insulin-like growth factor–binding protein 3, and improves somatic growth.

Introduction

Iodine is required for the production of thyroid hormones, which are essential for normal brain development, and the fetus and newborn are particularly vulnerable to iodine deficiency (1). In regions of severe endemic goiter, the adverse effects of *in utero* iodine deficiency on neuromotor development are well established: randomized controlled trials of iodine supplements given to iodine-deficient mothers before pregnancy or during early pregnancy improved motor and cognitive performance of their offspring (2–4). However, the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy are less clear.

Fetal and newborn hypothyroxinemia are the likely cause of brain damage due to iodine deficiency. Maternal thyroxine (T4) crosses the placenta to support neural development before onset of fetal thyroid function at 10–12 weeks (5). Maternal T4 represents up to 20–40% of T4 measured in cord blood at birth (6). Maternal subclinical hypothyroidism [an increased thyroid-stimulating hormone (TSH) in the second trimester] and maternal hypothyroxinemia [a free T4 (FT4) concentration <10 percentile at 12-week gestation] are associated with impaired mental/psychomotor development of the offspring (7,8). However, in these studies, the maternal thyroid abnormalities were not apparently due to iodine deficiency.

Iodine Requirements in Pregnancy

The iodine requirement during pregnancy is increased due to an increase in maternal T4 production to maintain maternal euthyroidism and transfer of thyroid hormone to the fetus, and iodine transfer to the fetus, particularly in later gestation (9). There may also be an increase in renal iodine clearance during pregnancy, although this is unclear (10,11). Several methods have been used to estimate iodine requirements in pregnancy. The thyroidal iodine accumulation by the infant at delivery has been used to estimate the daily fetal iodine uptake. Added to the estimated average requirement (EAR) of 95 μg/day for nonpregnant women, a daily fetal thyroid iodine uptake of ≈75 μg/day would suggest an EAR of 170 μg/day for pregnancy (12). Dworkin *et al.* (13) reported that pregnant women were in iodine balance when consuming ≈160 μg/day. In the United States, the EAR for iodine has been set at 160 μg/day for pregnant women

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Table 1. The WHO Daily Recommended Nutrient Intake for Iodine Proposed for Pregnant Women and the Excessive Daily Intake (Ref. 15), and the U.S. Institute of Medicine (IOM) Estimated Average Requirement and Recommended Dietary Allowance (Ref. 12) for Pregnant Women

Organization	*μg/day*
WHO (2006)	
Recommended nutrient intake	250
Excessive intake	500
U.S. IOM (2001)	
Estimated average requirement (EAR)	160
Recommended dietary allowance (RDA)	220

≥14 years, and the recommended dietary allowance, set at 140% of the EAR rounded to the nearest 10 μg, is 220 μg/day (Table 1) (12). In 2001, World Health Organization (WHO)/International Council for Control of Iodine Deficiency Disorders (ICCIDD)/United Nations International Children's Emergency Fund (UNICEF) recommended a daily iodine intake of 200 μg for pregnant women (14). However, a recent WHO technical consultation has increased the recommended iodine intake for pregnant women to 250 μg/day (Table 1) (15).

Defining "Mild-to-Moderate" Iodine Deficiency in Pregnancy

The median urinary iodine concentration (UI) is recommended by WHO/ICCIDD/UNICEF (14) for assessing iodine nutrition in populations. Daily iodine intake can be extrapolated from UI assuming median 24-hour urine volumes for girls aged 7–15 years of 0.9 mL/(hr kg) (16), and for adult women of ≈1.5 L (17). Assuming a mean iodine bioavailability of 92% and a modest increase in renal iodine clearance during pregnancy (10,11,18), recommended daily iodine intakes for pregnancy of 200–250 μg (12,14,15) correspond to a median UI of ≥150 μg/L in adult pregnant women (15). New recommendations from WHO state a median UI of 150–250 μg/L, which indicates adequate iodine intake in pregnancy (Table 2) (15). Thus, mild-to-moderate deficiency in pregnancy can be defined as a median UI of 50–150 μg/L. In National Health and Nutrition Examination Survey III (NHANES III), among pregnant women in the United States, 7% had a spot UI <50 μg/L (19). However, this should be interpreted with caution, as spot UIs tend to overestimate low and high intakes in a population (20). Moreover, among 15- to 44-year-old women in NHANES III, including pregnant women, there were no differences in TSH or T4 comparing those with a UI <50 μg/L and those with higher values (21).

Table 2. The Median or Range in Urinary Iodine Concentrations Used to Categorize the Iodine Intake of Pregnant Women (Data from Ref. 15)

Population group	*Median urinary iodine concentration (μg/L)*	*Category of iodine intake*
Pregnant women	<150	Insufficient
	150–249	Adequate
	250–499	More than adequate
	≥500	Excessive

Newborn TSH Concentrations Are a Sensitive Indicator of Iodine Nutrition during Pregnancy

Along with determination of the median UI in pregnant women, TSH screening in newborns may be useful in assessing iodine status in late pregnancy (22–27). In iodine-sufficient populations in Australia and Canada, the prevalence of elevated TSH concentrations (>5 mU/L, with the use of a sensitive monoclonal antibody assay) in blood filter paper specimens collected ≥3 days after birth was between 3% and 5% (23). However, multiple factors other than maternal iodine status can influence measurements of TSH concentrations in newborns, including timing of specimen collection, maternal or newborn exposure to iodine-containing antiseptics, and the TSH assay and collection paper used (26). Because of these uncertainties, the cutoffs for defining severity of iodine deficiency on the basis of newborn TSH concentrations originally proposed by the WHO (28) were not included in the most recent recommendations (14,15).

In Switzerland, because of declining iodine intakes in children and pregnant women, the iodine concentration in table salt was increased from 15 to 20 mg/kg in 1999. A recent prospective national study has evaluated UI in pregnant women, 5 years after the increase in the salt iodine concentration. In addition, the frequency of elevated TSH concentrations found in the newborn screening program was evaluated before and after the increase (29). In this program, whole-blood samples obtained on day 3 or 4 (72–96 hours) after birth are spotted and dried on filter paper and sent to a central laboratory. In 1999, before the salt iodine increase, the median UI among pregnant women was 138 μg/L, suggesting mild iodine deficiency. In 2004, median UI in pregnancy had increased significantly to 249 μg/L, indicating sufficiency. In 1992–1998, when iodine status was marginal in Switzerland, the prevalence of newborn TSH concentrations >5 mU/L was 2.9% ($n = 259{,}035$). After the increase in salt iodine content, the prevalence decreased to 1.7% in 1999–2004 ($n = 218{,}665$) ($p < 0.0001$) (Table 3). Thus, an increase in iodine concentration in iodized table salt markedly improved iodine status of pregnant women in Switzerland, and this improvement was reflected in the reduced frequency of newborn TSH values >5 mU/L. These data suggest that newborn TSH, obtained with the use of a sensitive assay on samples collected 3–4 days after birth, is a sensitive indicator of iodine nutrition during pregnancy (29). These data also support the original WHO recommendation that a <3% frequency of TSH values >5 mU/L indicates iodine sufficiency in a population (28).

Mild-to-Moderate Iodine Deficiency in Pregnancy: Intervention Studies

In Europe, six randomized controlled trials of iodine supplementation in pregnancy have been published, involving 450 women with mild-to-moderate iodine deficiency (30–35). Romano *et al.* (30) gave 120–180 μg iodine as iodized salt or control daily beginning in the first trimester to healthy pregnant women ($n = 35$; median UI = 31–37 μg/L). In the treated group, median UI increased threefold and thyroid volume did not change. In the controls, there was no change

Table 3. Newborn Thyrotropin Concentrations (Days 3 and 4 after Birth) from the Newborn Screening Program for Eastern Switzerland in 1992–1998 (before the Increase in Salt Iodine Concentration from 15 to 20 mg/kg) Compared with 1999–2004 (after the Increase) (Data from Ref. 29)

	Study year 1992–1998 (n = 259,035)	*Study year 1999–2004 (n = 218,665)*
Newborn whole-blood TSH (mU/L)[a]	1.2 (0.8–1.9)	1.2 (0.8–1.8)
Prevalence of newborn TSH >5 mU/L (%)	2.9	1.7[b]

[a]Median; interquartile range in parentheses (all such values).
[b]Significantly different from 1992–1998, $p < 0.0001$ (chi-square test).

in UI, but a 16% increase in thyroid volume. Treatment had no effect on maternal TSH. Pedersen *et al.* (31) randomized pregnant women ($n = 54$) to receive either 200 μg iodine/day as potassium iodide solution or no supplement from 17 weeks to term. Median UI increased from 55 μg/L to 90–110 μg/L in treated group. Maternal thyroid volume increased 16% in the treated group versus 30% in controls. Maternal serum thyroglobulin (Tg) and TSH, and cord Tg were significantly lower in the treated group. No significant differences were found between groups when maternal or cord T4, triiodothyronine (T3), and FT4 were compared. In a double-blind, placebo-controlled trial, Glinoer *et al.* (32) supplemented pregnant women ($n = 120$; median UI = 36 μg/L; biochemical criteria of excess thyroid stimulation) with 100 μg iodine/day or control from ~14 weeks to term. Treatment had no significant effect on maternal or cord T3, FT4, and T3/T4 ratio. The treated women had significantly higher UI, smaller thyroid volumes, and lower TSH and Tg concentrations, compared to controls. Newborns of the treated group also had significantly higher UI, smaller thyroid volumes, and lower Tg concentrations compared to controls.

Liesenkötter *et al.* (33) reported results from a controlled trial of 230 μg iodine/day from 11 weeks to term in pregnant women ($n = 108$; median UI 53 μg/g creatinine (cr); goiter rate 43%). Median UI increased to 104 μg/g cr in the treated group, and median thyroid volume was significantly lower in the newborns of the treated women compared to controls (0.7 mL vs. 1.5 mL, respectively). Treatment had no significant effect on maternal TSH, T3, T4, thyroid volume, or Tg, and had no effect on newborn TSH. In a placebo-controlled, double-blind trial, Nohr *et al.* (34) gave a multinutrient supplement containing 150 μg iodine/day or control to pregnant women positive for antithyroid peroxidase antibodies ($n = 66$) from 11 weeks to term. Median UI was significantly higher in the treated women at term, but there were no differences in maternal TSH, FT4, or Tg between groups. In a prospective, randomized, open-label trial, Antonangeli *et al.* (35) supplemented pregnant women ($n = 67$; median UI 74 μg/g cr) with 50 μg or 200 μg iodine/day from 18–26 weeks to 29–33 weeks. Median UI was significantly higher in the 200 μg group than in the 50 μg group (230 μg/g cr vs. 128 μg/g cr). However, there were no differences in maternal FT4, free T3 (FT3), TSH, Tg, or thyroid volume between groups.

Summarizing the results of these trials (30–35), supplementation significantly increased maternal UI in all studies. Iodine doses varied between 50 and 230 μg/day, and the data indicate no clear dose–response relationship for UI, TSH, Tg, thyroid hormones, or thyroid volume. In three of the five trials that measured maternal thyroid volume, supplementation was associated with significantly reduced maternal thyroid size, and the data also suggest an increase in newborn thyroid volume and Tg can be prevented or minimized by supplementation. The data are equivocal for an effect on maternal TSH; values are generally lower (within the normal reference range) with iodine supplementation. It is important to point out that in these mild-to-moderately iodine-deficient pregnant women, supplementation had no effect on maternal and newborn total or free thyroid hormone concentrations (36). Moreover, there are no clinical data on the effect of iodine supplementation on birth outcomes, and no data on long-term outcomes, such as maternal goiter, thyroid autoimmunity, or child development.

Moderate Iodine Deficiency Adversely Affects Cognition in Children

Globally, 35% of schoolchildren, or 285 million children, have inadequate iodine intakes (37). Although the adverse effects of iodine deficiency *in utero* on neuromotor development of the offspring are well established (2–4), the postnatal effects of iodine deficiency on cognitive function are less clear. Observational studies of children living in iodine-deficient areas have generally found evidence of impaired intellectual function and fine motor skills compared to children in iodine-sufficient areas (38–40). From a meta-analysis of these and other studies, it has been estimated that populations with chronic iodine deficiency experience a reduction of 13.5 points in intelligence (41). Although this evidence is suggestive, observational studies are often confounded by other environmental factors that affect child development, such as health, socioeconomic status, and the accessibility and quality of education (42). Moreover, these studies could not distinguish between the persistent effects of *in utero* iodine deficiency and the effects of current iodine status. Several randomized trials have examined the impact of iodine supplementation on the cognitive performance of children, but their results are equivocal, and methodological problems limit their interpretation (43–49).

Thus, although school-age children are a main target group of iodine prophylaxis (14), the benefits of iodine repletion in this age group are unclear. For a child born and raised under conditions of iodine deficiency, is iodine treatment beneficial? The aim of a recent study was to determine whether providing iodized oil to iodine-deficient children would affect their cognitive and motor performance (50). In a double-blind intervention trial, 10- to 12-year-old children ($n = 310$) in rural primary schools in southeastern Albania were randomized to receive either 400 mg of iodine as oral iodized oil or placebo. UI, thyroid functions, and thyroid gland volume were measured. The children were given a battery of seven cognitive and motor tests that included measures of information processing, working memory, visual problem solving, visual search, and fine motor skills. Thyroid ultrasound and the biochemical and psychological tests were repeated after 24 weeks. At baseline, the children had a median UI

of 43 μg/L, and 87% were goitrous. Although mean total T4 (TT4) was within the normal range, nearly one-third of the children had low levels of TT4. Treatment with iodine markedly improved iodine and thyroid status: at 24 weeks, median UI in the treated group was 172 μg/L, mean TT4 increased ≈40%, and the prevalence of hypothyroxinemia was <1%. Compared to placebo, iodine treatment significantly improved performance on four out of seven tests: rapid target marking, symbol search, rapid naming, and Raven's matrices ($p < 0.0001$) (Table 4). These findings suggest that information processing, fine motor skills, and visual problem solving are improved by iodine repletion in moderately iodine-deficient school-age children (50).

Moderate Iodine Deficiency Impairs Growth in Children

Severe iodine deficiency *in utero* causes cretinism and dwarfism (14). Iodized oil given during pregnancy in areas of moderate iodine deficiency increases birth weight (51,52). Less clear is the relationship between iodine deficiency and postnatal growth. Data from cross-sectional studies on iodine intake and child growth are mixed (53–58), with most studies finding modest positive correlations. In five Asian countries, household access to iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in infancy (59). However, controlled intervention studies of iodized oil alone (60,61) and iodine given with

Table 4. Age, Concentrations of Urinary Iodine, Whole-Blood Thyroid-Stimulating Hormone (TSH), Serum Total Thyroxine (TT4), Insulin-Like Growth Factor (IGF)-1, Insulin-Like Growth Factor–Binding Protein (IGFBP)-3, Height- and Weight-for-Age *z*-Scores, and Cognitive and Motor Tests in 10- to 12-Year-Old Albanian Children at Baseline and 6 Months after Receiving Either 400 mg of Iodine as Oral Iodized Oil or Placebo (Data from Refs. 50 and 80)

Variable	*Time (months)*	*Iodine*	*Control*
N		159	151
Age (years)[a]		11.3 ± 0.8	11.5 ± 0.8
Urinary iodine (μg/L)[b,c]	0	42 (0–186)	44 (0–215)
	6	172 (18–724)[e,h]	49 (3–221)
TSH (mU/L)[b]	0	1.6 (0.6–5.0)	1.8 (0.8–5.2)
	6	1.4 (0.4–5.2)	1.6 (0.4–15.4)
TT4 (nmol/L)[a,c]	0	76 ± 17	75 ± 17
	6	106 ± 18[f,i]	81 ± 19
Growth			
IGF-1 (ng/mL)[b,c]	0	147 (25–587)	139 (25–540)
	6	229 (71–627)[f,g]	178 (73–497)[d]
IGFBP-3 (μg/mL)[b,c]	0	3.1 (1.8–5.5)	3.3 (1.9–5.4)
	6	4.5 (1.0–7.2)[d,g]	3.7 (1.9–5.7)
Height-for-age *z*-score[b,c]	0	−1.17 (−4.33 to −1.22)	−1.08 (−3.69 to −2.23)
	6	−0.82 (−3.94 to −1.48)[d,g]	−1.03 (−3.61 to −1.83)
Weight-for-age *z*-score[b,c]	0	−0.77 (−2.77 to −0.91)	−0.83 (−2.68 to −1.92)
	6	− 0.53 (−2.74 to − 1.36)[d,g]	−0.70 (−2.58 to −2.22)
Cognitive and motor tests			
Ravens matrices[j]	0	17.0 ± 5.4	19.9 ± 6.3
	6	24.0 ± 6.3	20.5 ± 5.6
Adjusted treatment effect (95% CI)		4.7 (3.8, 5.8)	
Rapid target marking[j]	0	37.0 ± 12.6	34.2 ± 10.8
	6	29.5 ± 6.6	31.0 ± 7.2
Adjusted treatment effect (95% CI)		2.8 (1.6, 4.0)	
Symbol search[j]	0	17.3 ± 5.2	19.7 ± 4.8
	6	21.8 ± 4.5	20.5 ± 5.2
Adjusted treatment effect (95% CI)		2.8 (1.9, 3.6)	
Rapid naming[j]	0	52.9 ± 15.1	49.9 ± 16.6
	6	42.5 ± 10.6	45.2 ± 13.5
Adjusted treatment effect (95% CI)		4.5 (2.3, 6.6)	

[a]Mean ± SD.
[b]Median (range).
[c]Significant interaction (time × treatment) (ANOVA); $p < 0.0001$.
[d–f]Different from baseline (paired Wilcoxon test); [d]$p < 0.05$; [e]$p < 0.001$; [f]$p < 0.01$.
[g–i]Different from control (unpaired Wilcoxon test); [g]$p < 0.05$; [h]$p < 0.001$; [i]$p < 0.01$.
[j]Significant differences by mixed model ANOVA ($p < 0.0001$), adjusted for baseline, school, and gender. Baseline value was used as a fixed effect.

other micronutrients (62–64) have generally not found effects on child growth.

Iodine status may influence growth through its effects on the thyroid axis. Administration of T4 to hypothyroid children increases their growth (65). Thyroid hormone promotes growth hormone (GH) secretion and modulates the effects of GH at its receptor (66–68). Insulin-like growth factor (IGF)-1 and insulin-like growth factor–binding protein (IGFBP)-3 are also dependent on thyroid status (69–73). In humans, hypothyroidism decreases circulating IGF-1 and IGFBP-3 levels, and thyroid hormone replacement increases them (74,75). In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with IGF-1 and IGFBP-3 concentrations (76–78). However, in an uncontrolled trial, oral iodized oil decreased IGF-I and IGFBP-3 concentrations in Turkish children (79). The aim of a recent study (80) was to determine whether iodine repletion improves growth in school-age children, and to investigate the role of IGF-1 and IGFBP-3 in this effect. Three prospective, double-blind intervention studies were done: (i) in a 10-month study, severely iodine-deficient, 7- to 10-year-old Moroccan children ($n = 71$) were provided iodized salt and compared to children not using iodized salt; (ii) in a 6-month study, moderately iodine-deficient, 10- to 12-year-old Albanian children ($n = 310$) were given 400 mg iodine as oral iodized oil or placebo; (iii) in a 6-month study, mildly iodine-deficient 5- to 14-year-old South African children ($n = 188$) were given two doses of 200 mg iodine as oral iodized oil or placebo. At baseline and follow-up, height, weight, UI, TT4, TSH, and IGF-I were measured; in Albania and South Africa, IGFBP-3 was also measured. In all three studies, iodine treatment increased median UI to $>100\ \mu g/L$, while median UI in the controls remained unchanged. In South Africa, iodine repletion modestly increased IGF-1, but did not have a significant effect on IGFBP-3, TT4, or growth. In Albania and Morocco, iodine repletion significantly increased TT4, IGF-1, IGFBP-3, weight-for-age *z*-scores, and height-for-age *z*-scores (Table 4). This is the first controlled study to clearly demonstrate that iodine repletion in school-age children increases IGF-1 and IGFBP-3 concentrations and improves somatic growth (80).

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