iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review1–4

Michael B Zimmermann

ABSTRACT
The World Health Organization (WHO) recently increased their recommended iodine intake during pregnancy from 200 to 250 μg/d and suggested that a median urinary iodine (UI) concentration of 150–249 μg/L indicates adequate iodine intake in pregnant women. Thyrotropin concentrations in blood collected from newborns 3–4 d after birth may be a sensitive indicator of even mild iodine deficiency during late pregnancy; a <3% frequency of thyrotropin values >5 mU/L indicates iodine sufficiency. New reference data and a simple collection system may facilitate use of the median UI concentration as an indicator of iodine status in newborns. In areas of severe iodine deficiency, maternal and fetal hypothyroxinemia can cause cretinism and adversely affect cognitive development in children; to prevent fetal damage, iodine should be given before or early in pregnancy. Whether mild-to-moderate maternal iodine deficiency produces more subtle changes in cognitive function in offspring is unclear; no controlled intervention studies have measured long-term clinical outcomes. Cross-sectional studies have, with few exceptions, reported impaired intellectual function and motor skills in children from iodine-deficient areas, but many of these studies were likely confounded by other factors that affect child development. In countries or regions where <90% of households are using iodized salt and the median UI concentration in school-age children is <100 μg/L, the WHO recommends iodine supplementation in pregnancy and infancy. Am J Clin Nutr 2009;89(suppl):668S–72S.

IODINE REQUIREMENTS IN PREGNANCY
Iodine turnover, thyroidal radiiodine uptake, and balance studies suggest that the average daily requirement for iodine in nonpregnant women is 91–96 μg/d (1). The US Estimated Average Requirement (EAR) for iodine for nonpregnant, nonlactating women aged ≥14 y is 95 μg/d, and the Recommended Dietary Allowance—defined as the EAR plus twice the CV in the population— is 150 μg/d (1). This agrees with the WHO/ICCIDD/UNICEF Recommended Nutrient Intake for iodine of 150 μg/d for nonpregnant women (2). The iodine requirement during pregnancy (3) is sharply elevated 1) because of an increase by ≈50% in maternal thyroxine (T₄) production to maintain maternal euthyroidism and to transfer thyroid hormone to the fetus; 2) because iodine needs to be transferred to the fetus for fetal thyroid hormone production, particularly in later gestation; and 3) because of a probable increase in renal iodine clearance (RIC). The US EAR is 160 μg/d for pregnancy in women aged ≥14 y, and the Recommended Dietary Allowance, set at 140% of the EAR rounded to the nearest 10 μg, is 220 μg/d (1). Recently, the WHO/UNICEF/ICCIDD increased the Recommended Nutrient Intake for iodine during pregnancy from 200 to 250 μg/d (2), but emphasized the need for more data on the level of iodine intake [and the corresponding urinary iodine (UI) concentration] that ensures maternal and newborn euthyroidism.

INDICATORS OF IODINE STATUS DURING PREGNANCY AND INFANCY
Maternal urinary iodine concentration
The median UI concentration is recommended by the WHO (3) for assessing iodine intake in populations of nonpregnant and pregnant women. Daily iodine intake can be extrapolated from the UI concentration assuming 24-h urine volumes and iodine bioavailability of 92% (1); the recommended daily iodine intake during pregnancy of 220–250 μg (1, 2) would correspond to a median UI concentration of 135–155 μg/L during pregnancy. Pregnancy may occur in adolescence, particularly in developing countries; in a 15 y-old girl weighing ≈50 kg, a daily iodine intake of 200–250 μg would correspond to a UI concentration of ≈200 μg/L. However, during pregnancy this extrapolation of iodine intake from the UI concentration may be less valid because of an increase in RIC (3). If RIC increases in pregnancy, the daily iodine intake extrapolated from the UI concentration in pregnancy would be lower than that in nonpregnancy. More reference data on UI concentrations in chronically iodine-sufficient pregnant women, including trimester-specific values, would be valuable. The WHO currently recommends that a median UI concentration in a population of pregnant women of 150–249 μg/L indicates adequate iodine intake (Table 1). However, this population indicator should

1 From the Human Nutrition Laboratory, Swiss Federal Institute of Technology Zürich, Switzerland, and the Division of Human Nutrition, Wageningen University, Wageningen, Netherlands.
3 Supported by the Swiss Foundation for Nutrition Research and the Swiss Federal Institute of Technology (Zurich, Switzerland).
4 Reprints not available. Address correspondence to M Zimmermann, Human Nutrition Laboratory, Swiss Federal Institute of Technology Zentrum, Schmelzbergstrasse 7, LFV E19, CH-8092 Zürich, Switzerland. E-mail: michael.zimmermann@ilw.agrl.ethz.ch.
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iodine status in this age group (8). The system may facilitate the use of the UI concentration as an in-week after birth. These reference data and a simple collection for iodine sufficiency in infancy may be too high for the first concentration gradually increased within the range of 70–100 concentration was 77 (95% CI: 76, 81) feeding Swiss infants aged 0–5 d (7). To clarify this, UI concentrations were recently measured from this to a median UI concentration assuming a urine volume of 300–500 mL/d would produce a higher cutoff of 180 μg/L (7). The median UI concentrations were recently measured with a new pad collection system in a representative national sample of healthy, term, iodine-sufficient, euthyroid breast-feeding Swiss infants aged 0–5 d (n = 634) (8). The median UI concentration was 77 (95% CI: 76, 81) μg/L; the median UI concentration gradually increased within the range of 70–100 μg/L from days 1 to 4. Thus, the current WHO median UI cutoff for iodine sufficiency in infancy may be too high for the first week after birth. These reference data and a simple collection system may facilitate the use of the UI concentration as an indicator of iodine status in this age group (8).

TABLE 1

<table>
<thead>
<tr>
<th>Median urinary iodine (μg/L)</th>
<th>Iodine intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>Insufficient</td>
</tr>
<tr>
<td>150–249</td>
<td>Adequate</td>
</tr>
<tr>
<td>250–499</td>
<td>More than adequate</td>
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<tr>
<td>≥500</td>
<td>Excessive</td>
</tr>
</tbody>
</table>

1 Data are from reference 1.

iodine status in late pregnancy (4, 5). Recent data from a large representative Swiss study suggest that newborn thyrotropin concentrations, obtained with the use of a sensitive assay from blood samples collected 3–4 d after birth, is a sensitive indicator of even mild iodine deficiency in pregnancy (6) (Table 2). These findings support the WHO recommendation that a <3% frequency of thyrotropin values >5 mU/L indicates iodine sufficiency in a population (1). This finding should be confirmed in other iodine-sufficient countries with newborn screening programs. For UI, the WHO states that a median ≥100 μg/L in infants is sufficient (1). At the same time, they recommend an iodine intake of 90 μg/d during infancy (1), but extrapolating from this to a median UI concentration assuming a urine volume of 300–500 mL/d would produce a higher cutoff of ≥180 μg/L (7). To clarify this, UI concentrations were recently measured with a new pad collection system in a representative national sample of healthy, term, iodine-sufficient, euthyroid breastfeeding Swiss infants aged 0–5 d (n = 634) (8). The median UI concentration was 77 (95% CI: 76, 81) μg/L; the median UI concentration gradually increased within the range of 70–100 μg/L from days 1 to 4. Thus, the current WHO median UI cutoff for iodine sufficiency in infancy may be too high for the first week after birth. These reference data and a simple collection system may facilitate the use of the UI concentration as an indicator of iodine status in this age group (8).

TABLE 2

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Median urinary iodine (μg/L)</td>
<td>138</td>
<td>249</td>
</tr>
<tr>
<td>No. of newborns</td>
<td>259,035</td>
<td>218,665</td>
</tr>
<tr>
<td>Prevalence of thyrotropin &gt;5 mU/L in newborns (%)</td>
<td>2.9</td>
<td>1.7</td>
</tr>
</tbody>
</table>

1 Data are from reference 6.

not be used for the purposes of individual diagnosis and treatment—a common error.

Newborn thyrotropin and urinary iodine concentrations

Thyrotropin screening in newborns may be useful in assessing iodine status in late pregnancy (4, 5). Recent data from a large representative Swiss study suggest that newborn thyrotropin concentrations, obtained with the use of a sensitive assay from blood samples collected 3–4 d after birth, is a sensitive indicator of even mild iodine deficiency in pregnancy (6) (Table 2). These findings support the WHO recommendation that a <3% frequency of thyrotropin values >5 mU/L indicates iodine sufficiency in a population (1). This finding should be confirmed in other iodine-sufficient countries with newborn screening programs. For UI, the WHO states that a median ≥100 μg/L in infants is sufficient (1). At the same time, they recommend an iodine intake of 90 μg/d during infancy (1), but extrapolating from this to a median UI concentration assuming a urine volume of 300–500 mL/d would produce a higher cutoff of ≥180 μg/L (7). To clarify this, UI concentrations were recently measured with a new pad collection system in a representative national sample of healthy, term, iodine-sufficient, euthyroid breastfeeding Swiss infants aged 0–5 d (n = 634) (8). The median UI concentration was 77 (95% CI: 76, 81) μg/L; the median UI concentration gradually increased within the range of 70–100 μg/L from days 1 to 4. Thus, the current WHO median UI cutoff for iodine sufficiency in infancy may be too high for the first week after birth. These reference data and a simple collection system may facilitate the use of the UI concentration as an indicator of iodine status in this age group (8).

IODINE DEFICIENCY: THYROID ADAPTATION DURING PREGNANCY

Absorbed iodine (as iodide) from the diet mixes with circulating iodide from the peripheral deiodination of thyroid hormones; together they constitute the extrathyroidal pool of inorganic iodide (PII). This pool is in a dynamic equilibrium with the thyroid gland, together they constitute the extrathyroidal pool of inorganic iodide (PII). This pool is in a dynamic equilibrium with the thyroid gland, which takes up iodide for thyroid hormone synthesis, and with the kidneys, which filter and excrete iodide in the urine. In a healthy nonpregnant woman with adequate iodine intake, absorbed dietary iodine balances renal iodide clearance and the thyroid maintains normal iodine stores of 15–20 mg (3). A nonpregnant woman with a marginal iodine intake adapts by increasing thyrotropin stimulation of the thyroid; this may slightly increase thyroid size but can maintain iodine balance by increasing the thyroidal clearance of circulating PII and thereby decreasing RIC. However, if iodine intakes are chronically low, despite the decreased RIC, iodine balance becomes negative. To compensate for the missing dietary iodine, the thyroid must draw on its iodine stores to maintain euthyroidism, and they will be gradually depleted. If this woman becomes pregnant, she is suddenly faced with a ≥50% increase in iodine requirements because of a greater obligatory RIC and increasing requirements for thyroid hormone (3). With no thyroid iodine stores to draw from, progressive pathologic changes—goiter and hypothyroidism—can occur that can adversely affect maternal and fetal health (5).

IODINE DEFICIENCY: EFFECTS ON NEUROLOGIC DEVELOPMENT AND FUNCTION

Severe iodine deficiency during pregnancy causes maternal and fetal hypothyroxinemia (9). Thyroid hormone is required for normal neuronal migration, myelination, and synaptic transmission and plasticity during fetal and early postnatal life (10, 11), and hypothyroxinemia during these critical periods causes irreversible brain damage with mental retardation and neurologic abnormalities (12). The consequences depend on the timing and severity of the hypothyroxinemia. Two classic forms of cretinism—neurologic and myxedematous—have been described, but they can also occur in a mixed form (12). Whether mild-to-moderate maternal iodine deficiency produces more subtle changes in cognitive and/or neurologic function in the offspring is uncertain. However, 2 prospective case-control studies using different measures of impaired maternal thyroid function have reported developmental impairment in the offspring of affected mothers (13, 14), even if maternal hypothyroidism is mild and asymptomatic. Interpretation of these studies is limited by their case-control design and the fact that they were conducted in iodine-sufficient populations (13, 14). It is unclear whether maternal hypothyroxinemia, subclinical hypothyroidism, or both occur in otherwise healthy pregnant women with mild-to-moderate iodine deficiency (see discussion below).

EFFECTS OF SEVERE MATERNAL IODINE DEFICIENCY ON THE OFFSPRING

The design of the landmark trial in Papua New Guinea (15, 16) was quasi-random in that alternate families received iodine oil injections or control saline injections. The pregnancy status of...
women was not confirmed; it was either recorded by asking them whether they were pregnant or checking their delivery dates against the time they received the injection. For cretinism diagnosed at 4 y of age, the relative risk (95% CI) in the iodine group was 0.27 (0.12, 0.60). For cretinism diagnosed at ~10 y of age, the RR (95% CI) was 0.17 (0.05, 0.58). However, in 6 of 7 cretins found in the iodine group, the mother was late in pregnancy at the time of treatment. The authors carried out a long-term follow-up study on a subsample of noncretinous children at 11 and 15 y of age (17) and found no significant differences in motor and cognitive function between the children born to supplemented families and those born to controls, but the study was probably too small to detect a difference.

In the Zaire trial, participants were pregnant women attending antenatal clinics in the Ubangi region—an area of severe iodine deficiency with a 4% cretinism rate (18, 19). Few details on randomization and blinding were provided. The treatment intervention was an iodized oil injection at the time of their first clinic visit. Women were on average 28 wk pregnant when they were treated. The control group received an injection of iodine-free vitamins. At 72 mo of age, the mean psychomotor development scores were significantly higher in the iodine group (0.91 ± 0.13) than in the control group (0.82 ± 0.14). Treatment resulted in far fewer children with low psychomotor scores (0.5% with a score ≤0.60 compared with 9.7% in the control group). However, ~50% of the subjects in both groups were lost to follow-up.

In a study in Xinjiang province in western China, an area of severe iodine deficiency and endemic cretinism, the participants were children ranging from newborns to 3 y of age and women at each trimester of pregnancy (20). Untreated children 1–3 y of age, studied when first seen, served as controls. The intervention involved the administration of oral iodized oil. Treatment in the third trimester of pregnancy or after delivery did not improve neurologic status, but head growth and developmental quotients improved slightly. The mean (± SD) developmental quotients at 2 y of age in the treated and untreated children were 90 ± 14 and 75 ± 18, respectively. A small subsample was followed-up until 7 y of age (21). Iodine supplementation before the third trimester predicted higher psychomotor test scores for children than did iodine supplementation later in pregnancy or postnatally.

In a Peruvian trial (22, 23), the subjects were women of childbearing age from 3 Andean villages. The treatment group received iodized oil injection either before conception or during pregnancy. No details on randomization and blinding were provided, and the control group did not receive an injection. Cognitive development scores were determined in a subsample between 1 and 4 y of age, and the initial publication did not report a difference in cognitive outcomes in children. A reanalysis reassigned children to 2 groups (iodine-deficient or iodine-sufficient) at the time of cognitive testing and found a significantly higher IQ score in the iodine-sufficient group (85.6 ± 13.9) than in the iodine-deficient group (74.4 ± 4.8) (23).

Studies by Fierro-Benitez et al were conducted in 2 villages in Ecuador; one village received iodine treatment, whereas the other served as an iodine-deficient control group (24). The participants were women of childbearing age, pregnant women, and children, and the percentage of the population receiving treatment with iodine was estimated to be ~90%. The treatment group received iodized oil injections at 4-y intervals over 2 decades, and a series of follow-up studies were performed to assess the effects in offspring (24, 25). No baseline evaluation was conducted in the 2 villages to allow comparison with later testing results. Two years after treatment began, the mean IQs measured in first- and second-grade children were higher in the treated village (102.9 and 97.4 for boys and girls, respectively) than in the control village (94.2 and 84.5 for boys and girls, respectively). Later studies reported that iodine supplementation early in pregnancy or before conception improved IQ scores: 83.7 ± 13.4 compared with 72.7 ± 14.0 in the treated and control children, respectively (25).

These 5 intervention trials were groundbreaking studies conducted under difficult conditions in remote areas (14–25). The Papua New Guinea study had the strongest design and clearly showed that iodine treatment in a population with high levels of endemic cretinism sharply reduces or eliminates the incidence of this condition. The Zaire and China trials report developmental scores that were 10–20% higher in young children born to mothers treated during pregnancy or before. The studies in Peru and Ecuador were less well controlled but also suggest modest cognitive benefits for infants and children of maternal iodine treatment. Although the data from the Zaire trial indicate that the correction of iodine deficiency, even at mid-to-late pregnancy, improves infant cognitive development, data from the other trials suggest greater benefits when iodine is given before or early in pregnancy.

**EFFECTS OF MILD-TO-MODERATE MATERNAL IODINE DEFICIENCY ON THE OFFSPRING**

Endemic cretinism is the extreme expression of the abnormalities in physical and intellectual development caused by iodine deficiency, but the cognitive deficits associated with iodine deficiency may not be limited to remote, severely iodine-deficient areas. Many authors have argued that even mild-to-moderate iodine deficiency in pregnancy, still present in many countries in Europe and worldwide, may affect the cognitive and motor function of children.

**Controlled iodine supplementation trials in pregnancy**

The controlled trials of iodine treatment in mild-to-moderately iodine-deficient pregnant women have not reported data on infant or child development. However, several reported measures that might be surrogate markers of future infant development, including maternal and newborn thyroid function. Romano et al (26) gave 120–180 µg iodine as iodized salt or a placebo daily, beginning in the first trimester, to healthy pregnant Italian women (n = 35; median UI: 31–37 µg/L). In the treated group, median UI increased 3-fold and thyroid volume did not change. In the control subjects, UI did not change, but thyroid volume increased by 16%. Treatment had no effect on maternal thyrotropin. Pedersen et al (27) randomly assigned pregnant Danish women (n = 54) to receive either 200 µg iodide as a potassium iodide solution or no supplement from 17 wk to term. Median UI increased from 55 to 90–110 µg/L in the treated group. Maternal thyroid volume increased by 16% in the treated group and by 30% in the control subjects. Maternal thyroglobulin and thyrotropin and cord thyroglobulin were significantly lower in the treated group. No significant differences in maternal or cord T₄, triiodothyronine (T₃), or free T₃ (FT₃) were found between groups.

In a double-blind, placebo-controlled trial, Glinno et al (28) supplemented pregnant Belgian women (n = 120; median UI 36
μg/L; biochemical criteria of excess thyroid stimulation) with 100 μg I/d or a placebo from ~14 wk to term. Treatment had no significant effect on maternal or cord T₃, FT₄, or the T₃/T₄ ratio. The treated women had significantly higher UI concentrations, smaller thyroid volumes, and lower thyrotropin and thyroglobulin concentrations than did the control subjects. Newborns in the treated group also had significantly higher UI concentrations, smaller thyroid volumes, and lower thyroglobulin concentrations than did the control subjects. Liesenkötter et al (29) reported results from a quasi-random, controlled trial of 230 μg I/d from 11 wk to term in pregnant German women (n = 108; median UI: 53 μg/g Cr; goiter rate: 42.5%). The median UI increased to 104 μg/g Cr in the treated group, and the median thyroid volume was significantly lower in the newborns of the treated women (0.7 mL) than in the control subjects (1.5 mL). Treatment had no significant effect on maternal thyrotropin, T₃, T₄, thyroid volume, or thyroglobulin or on newborn thyrotropin.

In a placebo-controlled, double-blind trial, Nohr et al (30) gave a multinutrient supplement containing 150 μg I/d or control to pregnant Danish women positive for antithyroid peroxidase antibodies (n = 66) from 11 wk to term. Median UI was significantly higher in the treated women at term, but there were no differences in maternal thyrotropin, FT₄, or thyroglobulin between groups. Finally, in a prospective, randomized, open-label trial, Antonangeli et al (31) supplemented pregnant Italian women (n = 67; median UI: 74 μg/g Cr) with 50 μg or 200 μg I/d from 18–26 wk to 29–33 wk. Median UI was significantly higher in the 200-μg group (230 μg/g Cr) than in the 50-μg group (128 μg/g Cr). However, there were no differences in maternal FT₄, T₃, thyrotropin, thyroglobulin, or thyroid volume between groups.

These studies suggest that in areas of mild-to-moderate iodine deficiency, the maternal thyroid is able to adapt to meet the increased thyroid hormone requirements of pregnancy. Although supplementation was generally effective at minimizing an increase in thyroid size during pregnancy, only 2 of the 6 studies reported that maternal thyrotropin was lower (within the normal reference range) with supplementation; none of the studies showed a clear effect of supplementation on maternal and newborn total or free thyroid hormone concentrations. Thyroid hormone concentrations may be the best surrogate biochemical marker for healthy fetal development (10). Thus, the results of these trials are reassuring. However, because none of the trials measured long-term clinical outcomes, such as maternal goiter or infant development, the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy remain unclear.

**Meta-analyses comparing cognitive function in iodine-deficient and iodine-sufficient areas**

The meta-analysis of Bleichrodt and Born (32) included 21 observational and experimental studies with a control group. All studies were in areas of moderate-to-severe iodine deficiency, 16 studies were in children, 4 included adults, and 2 included infants; the age range of the subjects was 2–45 y. The IQs of the iodine-sufficient groups were, on average, 13.5 points higher than those of the iodine-deficient groups. However, the studies included were of varying quality; much of the data came from poorly controlled observational studies, and only 6 of the articles cited were published in peer-reviewed journals.

In a study by Qian et al (33), the inclusion criteria were studies conducted in China that compared children (aged <16 y) from areas of severe deficiency with 3 groups: 1) children living in naturally iodine-sufficient areas, 2) children in deficient areas born after the introduction of iodine prophylaxis, and 3) children in iodine-deficient areas born before the introduction of iodine prophylaxis. The IQs were 12.45, 12.3, and 4.8 points greater in the 3 groups, respectively, than in the severely deficient group. The IQ of the children born >3.5 y after iodine prophylaxis was introduced was ~12 points greater than that of the severely deficient children. Although the groups were reported to be comparable socially, economically, and educationally, it is difficult to judge the quality of the studies reported in Chinese included in this meta-analysis. Despite the limitations of these 2 meta-analyses (32, 33), the overall conclusions were similar: the study population, particularly the children, with chronic, severe iodine deficiency had a mean reduction in IQ of 12–13.5 points.

**STRATEGIES TO PREVENT OR CORRECT IODINE DEFICIENCY IN PREGNANCY**

For nearly all countries, the primary strategy for sustainable elimination of iodine deficiency in pregnancy remains universal salt iodization (34). However, implementation of universal salt iodization is not always feasible, which may result in insufficient access to iodized salt for women of childbearing age and pregnant women. Iodine supplementation of these groups should be considered. WHO/UNICEF/ICCIDD recommends that countries assess their salt iodization programs and then decide whether supplementation is indicated (34). Highly populated countries should use disaggregated data and categorize areas of the country according to subnational (region, province, district, etc) data. To ensure an adequate iodine supply during pregnancy, women should ideally be provided with an ample iodine intake (≥150 μg/d) for a long period of time before conception to ensure plentiful intrathyroidal iodine stores. An adequate iodine supply should continue after parturition, because the iodine requirement of a woman who is fully breastfeeding her infant is likely even higher than that during pregnancy. In countries or areas where <90% of households are using iodized salt and the median UI concentration in schoolchildren is <100 μg/L, the recommendations for iodine

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tr>
<td><strong>Recommendations for iodine supplementation in pregnancy and infancy in areas where &lt;90% of the households are using iodized salt and the median urinary iodine concentration in schoolchildren is &lt;100 μg/L.</strong></td>
</tr>
<tr>
<td><strong>Women of childbearing age</strong></td>
</tr>
<tr>
<td><strong>Pregnant or lactating women</strong></td>
</tr>
<tr>
<td><strong>Iodine supplements should not be given to women who already received iodized oil during current pregnancy or up to 3 mo before current pregnancy started.</strong></td>
</tr>
</tbody>
</table>

*From reference 34.*
supplementation in pregnancy and infancy are shown in Table 3. (Other articles in this supplement to the Journal include references 35–39.)

No conflicts of interest were declared.

REFERENCES


38. Carlson SE. Docosahexaenoic acid supplementation in pregnancy and lactation. Am J Clin Nutr 2009;89(suppl):678S–84S.