Consequences of iodine deficiency and excess in pregnant women: an overview of current knowns and unknowns[1,2]

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ABSTRACT

Severe iodine deficiency during development results in maternal and fetal hypothyroidism and associated serious adverse health effects, including cretinism and growth retardation. Universal salt iodization is the first-line strategy for the elimination of severe iodine deficiency. Iodine supplementation is recommended for vulnerable groups in severely iodine-deficient regions where salt iodization is infeasible or insufficient. A recent clinical trial has informed best practices for iodine supplementation of severely iodine-deficient lactating mothers. Because of successful programs of universal salt iodization in formerly severely iodine-deficient regions around the world, public health concern has shifted toward mild to moderate iodine deficiency, which remains prevalent in many regions, especially among pregnant women. Observational studies have shown associations between both mild maternal iodine deficiency and mild maternal thyroid hypofunction and decreased child cognition. Iodine supplementation has been shown to improve indexes of maternal thyroid function, even in marginally iodine-deficient areas. However, no data are yet available from randomized controlled trials in regions of mild to moderate iodine insufficiency on the relation between maternal iodine supplementation and neurobehavioral development in the offspring; thus, the long-term benefits and safety of such supplementation are uncertain. Although it is clear that excessive iodine intake can cause alterations in thyroid function in susceptible individuals, safe upper limits for iodine intake in pregnancy have not been well defined. Well-designed, prospective, randomized controlled trials that examine the effects of iodine supplementation on maternal thyroid function and infant neurobehavioral development in mildly to moderately iodine-deficient pregnant women are urgently needed. In addition, clinical data on the effects of iodine excess in pregnant and lactating women are needed to inform current recommendations for safe upper limits on chronic iodine ingestion in general and on iodine supplementation in particular. *Am J Clin Nutr* 2016;104(Suppl):918S–23S.

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INTRODUCTION

Dietary iodine is an intrinsic component of thyroid hormone, and adequate thyroid hormone is necessary for normal development. For that reason, severe iodine deficiency causes major adverse health effects, especially in pregnant women and their offspring.

In 1990, the UN World Summit for Children established the global elimination of iodine deficiency as a goal (1). Programs of universal salt iodization, instituted in accordance with recommendations of the WHO and the Iodine Global Network (formerly the International Council for the Control of Iodine Deficiency Disorders), have substantially improved iodine nutrition worldwide. Consequently, severely iodine-deficient regions have become uncommon and public health concern has shifted toward mild to moderate iodine deficiency (2).

Iodine supplementation of pregnant women is recommended in many regions where mild to moderate maternal iodine deficiency is prevalent (3); however, there is uncertainty about both the long-term benefit and the safety of iodine supplementation in such regions, especially where maternal iodine deficiency is mild. In the present article, we first provide an overview of the current status of iodine nutrition globally. Next, with a focus on pregnancy, we briefly summarize and provide expert opinion on the effects and prevention of severe and mild to moderate iodine deficiency, as well as the effects of iodine excess. We also discuss areas of uncertainty, introduce evidence of note from the recent literature, and consider avenues for future research.

EPIDEMIOLOGY OF IODINE DEFICIENCY

Iodine deficiency is defined by the WHO in terms of population median urinary iodine concentration (UIC).[7] When the median UIC of school-age children is 50–99 μg/L, a population is considered mildly iodine deficient (4). Based primarily on surveys of UIC in school-age children, an estimated 12 countries have excessive iodine intake, 116 have adequate iodine nutrition,

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[7] Abbreviations used: TPO, thyroperoxidase; TSH, thyroid-stimulating hormone; T4, thyroxine; UIC, urinary iodine concentration.

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and 25 remain iodine deficient; of the latter, 7 are moderately deficient, 18 are mildly deficient, and none are considered severely deficient (5). Worldwide, an estimated 1.9 billion individuals are at risk of iodine deficiency (2).

The median UIC of school-age children may not reflect the iodine status of pregnant women in the same regions (6). This is especially true in areas in which dairy products are an important source of dietary iodine, because children typically consume more milk than women (7). Globally, national surveys of the iodine status of pregnant women are limited.

Mild to moderate iodine deficiency is common in Europe. Of the total population of ~590 million in this region, 350–400 million individuals currently have no access to iodized salt or are not using it even if available (8). More than half of European countries collect national data on iodine intakes in pregnant women; of these, two-thirds have reported low iodine intakes during pregnancy (9). The frequency of iodine supplementation in pregnancy varies and, even when supplementation is given, adequate iodine status (based on the median UIC of the pregnant women enrolled in the study) is not always attained. In Denmark, for example, after salt iodization, although most pregnant women reported taking iodine-containing supplements, pregnant women who did not take such supplements were at higher risk of being iodine deficient (median UIC of 68 compared with 109 μg/L in the supplemented women) (10). In Belgium, a national survey found that the median UIC in pregnancy, 124 μg/L, was below the WHO's recommended threshold of 150 μg/L, despite the fact that most pregnant women take iodine supplements (11). The Belgian survey also found that suboptimal iodine intake during pregnancy was associated with hyperstimulation of the thyroid, as indicated by higher serum thyroglobulin concentrations in the third trimester of pregnancy than in the first trimester (12). In the United Kingdom, where there is no salt iodization, regional surveys recently showed iodine deficiency in pregnant women (median UIC: 85 μg/L) (13) and adolescent girls (median UIC: 81 μg/L) (14); for the latter, the WHO's recommended threshold is 100 μg/L.

The United States has been iodine sufficient overall since the 1940s. However, in recent years, mild iodine deficiency has emerged among pregnant women. NHANES 2005–2010 data indicate that the median UIC across the pregnant US women sampled was 129 μg/L (15), which reflects a decrease from 153 μg/L in 2001–2006 (16). Although iodized salt is generally available in the United States, salt iodization is not mandatory.

SEVERE IODINE DEFICIENCY: EFFECTS AND PREVENTION

When the median UIC of school-age children is <20 μg/L, a population is considered severely iodine deficient (4). Severe iodine deficiency is associated with an array of adverse effects, including goiter, cretinism, neonatal hypothyroidism, growth retardation, and increased risks of pregnancy loss and infant mortality (17). Thyroid hormone is particularly critical for fetal and infant neurodevelopment. Brain development is dependent on adequate thyroid hormone, and severe iodine deficiency during pregnancy may result in maternal and fetal hypothyroidism and serious neurologic and cognitive deficits in children (18). In addition to the overt manifestations of severe iodine deficiency, apparently healthy children and pregnant women living in severely iodine-deficient regions may suffer from endemic hypothyroidism (19).

Severe iodine deficiency may be aggravated if goitrogens or their precursors are present in the staple food of the deficient regions. Goitrogens may impair thyroid function by decreasing the uptake of iodide by the thyroid; this is the primary goitrogenic action of thiocyanate, which is present in precursor form in cassava at high concentrations. Other goitrogens, such as the flavonoids present in millet, inhibit the activity of thyroperoxidase (TPO), an enzyme that catalyzes important steps in thyroid hormone synthesis (20). Millet and cassava are staple foods in many iodine-deficient regions of Africa. The public health impact of the interaction between iodine deficiency and goitrogens is strong, because severely iodine-deficient regions are usually isolated, with little food diversity; one example is the famine- and war-affected Darfur region of Sudan, where monotonous consumption of a goitrogenic diet exacerbates the adverse effects of iodine deficiency. In these regions, the population typically consumes only locally produced food items. In addition to the prevalence of goitrogens in the diet, dietary deficiencies of the micronutrients selenium, iron, and vitamin A may interact with iodine deficiency and affect the response of iodine-deficient subjects to iodine supplementation (17).

Universal salt iodization is recommended in iodine-deficient regions and has been shown clearly to improve maternal health and infant developmental outcomes. In severely iodine-deficient regions where salt iodization is infeasible or inadequate, the WHO recommends that oral supplementation, as either a low dose of iodine taken daily or a high dose of iodized oil taken every 6–12 mo, be given to pregnant and lactating women, women of reproductive age, and children under the age of 2 y (3).

Until lately, there was little evidence to support WHO recommendations that oral iodized oil be given to severely iodine-deficient breastfeeding mothers or to infants who are not being breastfed or receiving iodine-fortified complementary foods. Recently, however, a double-blind, randomized, placebo-controlled trial in Morocco assessed the safety and efficacy of direct compared with indirect supplementation of infants (21). Healthy breastfeeding mothers and their term newborn infants (aged ≤8 wk) were randomly assigned to receive either 1 dose of 400 mg I to the mother and placebo to the infant (indirect infant supplementation) or 1 dose of ~100 mg I to the infant and placebo to the mother (direct infant supplementation). At 6 mo of age, the median UIC for the indirectly supplemented infants was 142 compared with 122 μg/L in the directly supplemented infants ($P = 0.04$). The results show that in regions of moderate to severe iodine deficiency without effective salt iodization, lactating women who receive 1 dose of 400 mg I as oral iodized oil soon after delivery can provide adequate iodine to their infants through breast milk for ≥6 mo, enabling the infants to achieve euthyroidism. Thus, on the basis of the findings of that study with iodized oil, direct supplementation appears to be less effective in improving infant iodine status than indirect supplementation.

MILD TO MODERATE IODINE DEFICIENCY: EFFECTS AND PREVENTION

Mild to moderate iodine deficiency in a population, defined by median UIC values of 20–99 μg/L in school-age children (4),

increases thyroid volume and risk of goiter in the population overall and in pregnant women (22, 23). These effects can be prevented with iodine supplementation or iodine fortification of salt (24, 25). Serum thyroglobulin concentrations are positively correlated with thyroid volume in iodine-deficient regions (26), and mild to moderate iodine deficiency may be associated with elevated serum thyroglobulin concentrations in adults and children (26, 27). However, mild iodine deficiency is generally not associated with major alterations in serum thyroid function during pregnancy.

There is evidence that maternal iodine supplementation improves some maternal thyroid indexes even in marginally iodine-deficient areas. Nine randomized controlled trials of the effects of iodine supplementation on measures of thyroid function in pregnant women have been conducted to date in mildly to moderately iodine-deficient regions; results from these trials are summarized in Tables 1 and 2 of a recent systematic review by Taylor et al. (25). Three of 4 trials in which maternal serum thyroglobulin was assessed found lower concentrations in supplemented women than in controls, and 3 of 5 trials in which maternal serum thyroid-stimulating hormone (TSH) was assessed found lower concentrations in supplemented women than in controls.

There is also evidence that excessive iodine supplementation during pregnancy can increase serum TSH concentrations and thus have a negative impact on maternal thyroid function. In one observational study, pregnant women who self-reported ingesting supplements containing >200 μg I/d were found to be at increased risk of serum TSH elevation compared with women whose supplemental iodine intake was <100 μg/d (28). Another observational study showed higher serum TSH concentrations in women with a supplemental iodine intake of 150 μg/d starting in early pregnancy compared with women who used iodized salt starting 2 y before pregnancy and women without iodized salt or iodine supplement use (29). Only 3 clinical trials have assessed neonatal thyroid function in the offspring of supplemented women compared with nonsupplemented women, and these did not show any differences; results from the 3 trials are summarized in the systematic review by Taylor et al. (25).

It is not clear to what extent mild maternal iodine deficiency during pregnancy influences child neurobehavioral development (30). Although 2 observational studies have reported that mild maternal iodine deficiency during pregnancy is associated with either lower child intelligence quotient (31) or educational assessment (32) scores, there is conflicting information from observational studies with regard to the effects of maternal iodine supplementation on child neurobehavioral development in areas of mild iodine deficiency. One observational study found that supplemental iodine at ≥ 150 μg/d did not improve psychomotor or mental development in the infant offspring of either mildly iodine-deficient or iodine-sufficient pregnant women and may have adversely affected these outcome measures (33), whereas 2 other uncontrolled observational studies found a possible improvement in psychomotor development, but not mental development, with prenatal supplementation (34, 35). A randomized clinical trial conducted in a region of mild to moderate iodine deficiency evaluated psychomotor development in the offspring of 3 groups of pregnant women; 2 of the groups received supplemental iodine at either 200 or 300 μg/d and all of the groups were advised to use iodized salt in cooking and at the table (36). Because there was no nonintervention control group, the study's findings of no intergroup differences in the outcome measures assessed are not informative as to whether prenatal supplementation improves child neurodevelopment in such regions in the absence of advisory intervention regarding iodized salt use. To our knowledge, there are no data available from any randomized controlled clinical trial on the relation between prenatal iodine supplementation and child neurobehavioral development in regions of mild to moderate iodine deficiency.

On the basis of available information, several medical and public health advisory groups have recommended iodine supplementation for women who are pregnant, lactating, or planning a pregnancy (37–40), but these recommendations have not been widely adopted to date in most regions (41, 42). Apparently, many government health authorities have been reluctant to make broad recommendations for iodine supplementation in the absence of definitive evidence from randomized clinical trials.

EFFECTS OF MATERNAL SUBCLINICAL HYPOTHYROIDISM ON CHILD NEURODEVELOPMENTAL OUTCOMES: POTENTIAL ROLE OF IODINE DEFICIENCY

By analogy with the effects of severe iodine deficiency during pregnancy, it is presumed that any potential effects of mild to moderate maternal iodine deficiency on child neurodevelopment are mediated through some alteration of maternal thyroid function and possibly fetal thyroid function as well. Thyroxine (T4) is the primary circulating form of thyroid hormone. Several observational studies have reported associations between maternal hypothyroxinemia or subclinical hypothyroidism in pregnancy and decreased child cognition (43, 44) but did not establish a link to iodine deficiency. Thyroid function is a poorly sensitive index of population iodine status in adults (45), and it is not clear whether maternal subclinical hypothyroidism occurs more frequently in mildly to moderately iodine-deficient regions than it does in iodine-sufficient regions (40). However, isolated maternal hypothyroxinemia is found more frequently in pregnant women from mildly to moderately iodine-deficient regions than in those from regions that are iodine sufficient (46). A recent, prospective, randomized, multicenter clinical trial (the Antenatal Thyroid Screening and Childhood Cognitive Function Study) examined cognitive outcomes at age 3 y in the offspring of 2 groups of pregnant women with mild thyroid hypofunction early in pregnancy; one group was treated with levothyroxine during pregnancy and the other was not treated (47). The study recruited 21,846 pregnant women at a gestational age of ≤ 16 wk. After random assignment to screening and control groups, blood samples for thyroid function were measured immediately in the screening group but only after delivery in the controls. Abnormal thyroid function, defined as serum TSH above the 97.5th percentile or serum free T4 below the 2.5th percentile, or both, was the basis for selecting 390 women in the screening group, who received 150 μg levothyroxine daily, and 404 women in the control group, who received no therapy. The intelligence quotient of the children born of these 2 groups of women was assessed at age 3 y and did not differ. Although there was evidence of mild to moderate iodine deficiency in both the screening group and the control group, iodine supplementation of the screening group was not needed because treatment with levothyroxine ensured adequate serum free T4. It is probable that iodine deficiency was not the cause of the decreased thyroid function in the high-TSH group, given that

TPO antibody positivity (a hallmark of autoimmune thyroid disease) was present in 60% of the women (47). The effect of iodine prophylaxis on child cognition in subclinically hypothyroid women has not been studied.

EFFECTS OF IODINE EXCESS IN PREGNANCY

Excessive iodine intake can cause alterations in thyroid function in susceptible individuals (48). In normal individuals, high iodine exposure can cause transient inhibition of thyroid hormone synthesis by a mechanism known as the acute Wolff-Chaikoff effect (49). Typically, the thyroid "escapes" from the acute Wolff-Chaikoff effect within a few days through downregulation of the iodide transporter in thyroid cells, and normal thyroid hormone synthesis resumes (50, 51).

Failure of the "escape" can result in iodine-induced hypothyroidism (51). This is seen most frequently in those with Hashimoto thyroiditis. The ability to fully escape from the acute Wolff-Chaikoff effect does not mature until ~36 wk of gestation, and fetal hypothyroidism may develop in the setting of a large iodine load even if maternal thyroid function is maintained (52). By contrast, iodine-induced hyperthyroidism represents a failure of the acute Wolff-Chaikoff effect. It occurs most frequently in those with nodular goiters, which are more common in iodine-deficient regions (40).

The above effects have been described for very high iodine exposures associated with medical or diagnostic doses. Population increases in dietary iodine intake are found to be associated with increased prevalence of thyroid autoimmunity (53–55). A recent cross-sectional study conducted in China showed a U-shaped relation between thyroid function and UIC among 7190 women in the first trimester of pregnancy, with the lowest serum TSH and thyroglobulin values associated with UICs of 150–249 μg/L (56). For pregnant women, the Institute of Medicine recommends an iodine upper limit of 1100 μg/d (57), whereas the WHO more conservatively recommends an upper limit of 500 μg/d (58). The data from the above-described Chinese study suggest that the Institute of Medicine's recommended 1100 μg/d upper limit is too high.

DATA GAPS AND AREAS FOR FUTURE RESEARCH

Despite the fact that mild to moderate iodine deficiency remains prevalent in many regions (5), defining its potential deleterious effects on fetal neurobehavioral development is challenging. As discussed above, there is some evidence for an association between mild iodine deficiency during pregnancy and reduced cognitive or educational outcomes in children (31, 32). Assuming that such findings hold up and are indicative of causality, a role for maternal hypothyroxinemia might yet emerge. Another possibility is that currently defined "normal" thyroid hormone concentrations in mildly iodine-deficient women during pregnancy do not necessarily imply an optimal fetal brain supply of thyroid hormone. An alternate theory is that mild to moderate iodine deficiency can affect neurobehavioral development through thyroid-independent mechanisms, but this is unlikely.

The possibility of a cumulative effect of mild to moderate iodine deficiency during pregnancy and early infancy has implications for the design of maternal iodine supplementation trials. It might be important to follow the iodine status of the offspring from birth and to provide supplemental iodine to newborns and infants who are not receiving adequate iodine via nursing or otherwise.

Well-designed prospective, randomized controlled trials that examine the neurodevelopmental effects of iodine supplementation in mildly to moderately iodine-deficient pregnant women are urgently needed. One such trial is nearing completion: a randomized controlled trial in mildly iodine-deficient women in India and Thailand is investigating the effects of prenatal iodine supplementation on maternal thyroid function, pregnancy and birth outcomes, and infant cognitive and motor development (59). Healthy pregnant women aged 18–40 y with a gestational age of $<$12 wk are randomly assigned to receive either 200 μg potassium iodide or a placebo, daily until delivery. Follow-up has been completed on the infants at 2 and 5 y of age; a report from this trial is expected in 2016.

More data from controlled trials are clearly needed, but questions remain about how best to design and carry out future studies. The question arises as to whether it is ethically acceptable to include a placebo control group in mildly iodine-deficient regions. We believe that such studies are warranted and the use of a placebo control group is ethically acceptable, particularly in regions where iodine supplementation is not currently recommended in pregnancy, because to date there is no clear evidence that mild iodine deficiency during pregnancy has long-term adverse effects on maternal or offspring outcomes. The ethical acceptability of iodine supplementation in the treatment group is not in question because the only potential risks are alterations in thyroid function, which should be monitored within the setting of the trial. Such monitoring is important because of the possibility that some women enrolled in the trial will have very high dietary iodine intakes independent of the trial. In that case, the supplemental iodine they receive through the trial could put them at higher risk of thyroid function abnormalities associated with iodine excess.

Without additional data, it is hard to justify the high costs and logistical challenges of iodine supplementation of large numbers of pregnant women in mildly iodine-deficient areas around the world. Moreover, coverage of supplementation would likely be inequitable, reaching mainly higher socioeconomic strata, and may not be without risk of adverse effects on thyroid function. Thus, it should only be recommended globally if there is clear evidence of benefit.

Another area of future research should be the effect of concurrent micronutrient deficiencies, particularly iron and selenium, on iodine and thyroid status during pregnancy. Iron deficiency is common during the latter half of pregnancy (60), and cross-sectional studies have shown that poor maternal iron status predicts both higher serum TSH and lower serum total T4 concentrations during pregnancy in areas of borderline iodine deficiency (60, 61).

As noted by other authors in this supplement issue, a better understanding of the specific domains of cognitive and psychomotor development affected by iodine deficiency would be valuable (62, 63). Physical methods (e.g., MRI, electroencephalography, functional positron emission tomography, and magnetoencephalography) for measuring activity foci and functional networks in specific brain areas during the performance of cognitive tasks may provide data unconfounded by cultural and socioeconomic factors. In addition, better biomarkers of iodine

status at the individual level are needed to optimize the inclusion of mildly to moderately iodine-deficient subjects in clinical trials, a topic discussed by Pearce and Caldwell (64) elsewhere in this supplement issue. In the meantime, it may be wise to use several surrogate markers of iodine status (e.g., serum thyroglobulin, the serum ratio of triiodothyronine to T4, and thyroid volume) in addition to UIC to select pregnant women most affected by mild to moderate iodine deficiency.

Finally, more data are needed to inform recommendations about safe upper limits for chronic iodine ingestion in pregnant and lactating women. This will help with assessing the risks of iodine supplementation in these groups and with determining optimal dosing strategies.

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