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Iodine in Pregnancy: Is Salt Iodization Enough?

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Iodine deficiency affects more than 2.2 billion individuals worldwide (38% of the world's population). Decreases in maternal T₄ associated with even mild iodine deficiency may have adverse effects on the cognitive function of offspring (1,2), and iodine deficiency remains the leading cause of preventable mental retardation worldwide. It has recently been suggested that mild iodine deficiency may also be associated with attention-deficit and hyperactivity disorders in offspring (3).

Dietary iodine requirements are increased in pregnant women for several reasons. Maternal thyroid hormone production normally increases by about 50% during gestation, starting during the first trimester, due to human chorionic gonadotropin stimulation of the TSH receptor and because high estrogen levels induce an increase in the sialylation of T₄-binding globulin (TBG), leading to reduced hepatic TBG clearance and increased concentrations of circulating TBG (4,5). In addition, the peripheral metabolism of thyroid hormone may be increased, especially in the second half of pregnancy, due to placental deiodination of T₄ to the bioinactive reverse T₃ (6). By at least wk 10–12 of pregnancy, some maternal iodine stores are transferred to the fetus to allow for hormone production in the fetal thyroid; the amount of iodine transferred in this way is unclear (7). Finally, the glomerular filtration rate of iodide increases early in pregnancy, increasing renal iodide clearance and decreasing the circulating pool of plasma iodine (8). To compensate for renal iodine losses, there is an increased rate of uptake of iodine into the thyroid gland in pregnant women (7).

Women with adequate iodine intake before and during pregnancy have adequate intrathyroidal iodine stores and have no difficulty adapting to the increased demand for thyroid hormone during gestation. In these women, total body iodine levels remain stable throughout pregnancy (9). However, in areas of even mild to moderate iodine deficiency, total body iodine stores, as reflected by urinary iodine values, decline gradually from the first to the third trimester of pregnancy (10). This dietary iodine deficiency results in impaired thyroid hormone synthesis. Low thyroid hormone values stimulate increased pituitary TSH production, and the increased TSH stimulates thyroid growth, which may result in maternal goiter (11). This was so common in some parts of Europe that it used to be assumed, mistakenly, that goiter formation was a physiological response to pregnancy (12). Ultimately, iodine deficiency may result in maternal thyroid failure.

The introduction of iodized salt has been the mainstay of international iodine deficiency eradication efforts because it is an inexpensive source of stable iodine content, and salt is consumed in relatively similar quantities by individuals worldwide. In the current issue of the *Journal*, Moleti *et al.* (13) describe the effects of long-term and short-term iodized salt use on the risk for maternal thyroid failure in a cohort of pregnant women from Sicily. Women were enrolled during the first trimester of pregnancy, and their iodized salt use for the preceding 2 yr was retrospectively ascertained. Among 38 women who started using iodized salt only when they became pregnant, the prevalence of thyroid failure during pregnancy was remarkably high at 36.8%. Most of this thyroid failure consisted of hypothyroxinemia with normal serum TSH values. Although long-term iodized salt use reduced the risk for maternal thyroid failure 6-fold, 6.4% of the 62 women who consistently used iodized salt for at least 2 yr before

pregnancy also developed thyroid failure during pregnancy. First-trimester median urinary iodine excretion in both of these groups (115 $\mu\text{g}/\text{liter}$ in those with long-term iodized salt use and 63 $\mu\text{g}/\text{liter}$ in those with short-term iodized salt use) was below the World Health Organization's optimal pregnancy range of 150–249 $\mu\text{g}/\text{liter}$ (1).

It is important to note that a large proportion of potential subjects were excluded from this study because of baseline thyroid abnormalities such as autoimmune thyroiditis, nodular goiter, or baseline thyroid dysfunction. It is possible that these women would have been even more vulnerable to the effects of inadequate dietary iodine in pregnancy, and thus, the study may actually have underestimated the true effects of iodine replacement in an unselected population.

Another point worth noting is the use of trimester-specific TSH and free T_4 reference ranges derived from 500 consecutive healthy, thyroid antibody-negative, pregnant women from the local population. This is in line with recent recommendations (14), and the resulting ranges were similar to previously published studies from other regions (15,16,17). However, given the underlying iodine deficiency of the region studied, it is difficult to be sure that the derived reference ranges truly reflect normal thyroid function.

The U.S. Institute of Medicine's recommended dietary allowance for iodine is 220 $\mu\text{g}/\text{d}$ for pregnant women, higher than the 150 $\mu\text{g}/\text{d}$ recommended for nonpregnant adults and adolescents (18). Similarly, recent World Health Organization guidelines suggest an intake of 200–300 $\mu\text{g}/\text{d}$ iodine daily for pregnant women (1), and the Endocrine Society has recently recommended an average daily intake of 250 μg iodine daily for pregnant women (19). Based on their urinary iodine excretion, even the women in the Sicilian study who were long-term iodized salt users may have been falling short of these targets. Much of Western and Central Europe remains mildly to moderately iodine deficient (20), and even in the United States, there are concerns that a subset of women of child-bearing age may be mildly iodine deficient (21). How should these study results shape public policy in Italy and elsewhere?

Urinary iodine concentration thresholds have been identified for populations but not individual patients. For this reason, a public health approach to iodine supplementation has been advocated, particularly for pregnant women and women of child-bearing age. The study's authors suggest screening and monitoring of thyroid status in all pregnant women living in areas of known iodine deficiency to ensure timely introduction of L-thyroxine where needed. Although this is a reasonable short-term approach, it would be preferable and more cost effective to ensure population iodine sufficiency so that such measures would not be necessary for pregnant women (*i.e.* to target prevention rather than treatment of maternal thyroid failure).

One important lesson of this study is that long-term iodized salt use is highly beneficial for pregnant women. This reinforces our awareness that broad access to iodized salt is vital and that salt iodization programs need to target whole (not just vulnerable) populations; as this study elegantly demonstrates, by the time women become pregnant, it may be too late for iodized salt to be effective. In some parts of Europe, iodization of all table salt is already mandatory. In 2005, after the completion of this study, Italy enacted legislation that makes iodized table salt the default option at the point of sale; customers wishing to buy noniodized salt must specifically request it. This should increase the proportion of the Sicilian population using iodized table salt.

Was the amount of iodine in the table salt used by the study participants sufficient? Table salt in Italy is iodized at 30 ppm (potassium iodide or potassium iodate), which is typical of many European programs, although substantially lower than the 100 ppm potassium iodide fortification in the United States. The goal of salt iodization programs is to provide enough iodine to ensure sufficiency for the most vulnerable individuals without causing excessive iodine intake. Because there is some person-to-person variation in the amount of table salt consumed, perfectly achieving this balance can be difficult when only household salt is iodized. In Europe and the United States, most salt consumed is from commercially produced food products. Iodization of salt used in commercial food production as well as salt for household use may allow more uniform iodine consumption across populations. However, in many places this proposal has met with political or commercial opposition.

The optimal duration of adequate iodine nutrition before pregnancy is unknown. The 2-yr time period used in the Sicilian study was arbitrarily determined. Further studies are needed to better elucidate the time required to establish sufficient intrathyroidal iodine stores to maintain normal thyroid function in pregnancy.

Randomized controlled trials examining the use of iodine-containing dietary supplements for pregnant women from iodine-deficient regions have demonstrated increased maternal urinary iodine concentrations, decreased maternal and neonatal thyroid volumes, and decreased maternal serum TSH concentrations (20). Although the World Health Organization has recommended 250 µg daily iodine supplements for pregnant women in areas with insufficient access to iodized salt (1), only approximately 15–30% of pregnant women in Europe currently receive iodine-containing supplements (20). The American Thyroid Association has also recently recommended that North American women receive dietary supplements containing 150 µg iodine daily during pregnancy and lactation and that all prenatal vitamins contain 150 µg of iodine (22), recommendations that have not been adopted. Given the limitations of inadequate or short-term iodized salt use in preventing maternal thyroid failure, frequent population monitoring needs to be carried out, even in regions with salt iodization programs, to identify areas in which pregnant women and their offspring may be at risk. Whereas salt iodization programs remain essential, the addition of adequate iodine-containing prenatal multivitamins should be strongly encouraged for women from regions of even borderline iodine deficiency who are pregnant or planning to become pregnant.

Footnotes

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Abbreviation: T₄, Thyroxine-binding globulin.

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