Teratology Public Affairs Committee Position Paper: Iodine Deficiency in Pregnancy

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Iodine deficiency is an important nutritional deficiency, with more than 2 billion people worldwide estimated to be at risk. The developing fetus and young children are particularly at risk. During pregnancy and lactation, iodine requirements increase, whether in iodine-poor or iodine-sufficient countries, making the mother and the developing fetus vulnerable. The American Thyroid Association (ATA) recommends 250 micrograms per day of iodine intake for pregnant and lactating women. The thyroid gland is able to adapt to the changes associated with pregnancy as long as sufficient iodine is present. Dietary intake is the sole source of iodine, which is essential to the synthesis of thyroid hormones. Iodine is found in multiple dietary sources including iodized salt, dairy products, seaweed, and fish. Prenatal vitamins containing iodine are a good source of iodine, but iodine content in multivitamin supplements is highly variable. Congenital hypothyroidism is associated with cretinism. Clinical hypothyroidism has been associated with increased risk of poor perinatal outcome including prematurity, low birth weight, miscarriage, preeclampsia, fetal death, and impaired fetal neurocognitive development. Subclinical hypothyroidism is also associated with poor pregnancy outcomes and potential fetal neurocognitive deficits, but the data are more variable than those for clinical hypothyroidism. We concur with the ATA recommendation that all pregnant and lactating women should ingest (through diet and supplements) 250 micrograms of iodine daily. To achieve this goal, we recommend that all pregnant and lactating women take daily iodine supplementation of 150 micrograms. *Birth Defects Research (Part A) 94:677–682, 2012.* © 2012 Wiley Periodicals, Inc.

Key words: iodine deficiency; pregnancy; iodine supplementation; thyroid hormones; lactation; pregnancy complications; child development

SCOPE OF THE PROBLEM

Iodine is an essential element in the synthesis of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), by the thyroid gland. Dietary intake is the sole source of iodine. Beginning in the first trimester of pregnancy, there is an increase in the requirement for maternal production of thyroid hormones and a resultant need for an increase in iodine uptake by the thyroid gland. After conception, maternal thyroid hormone production increases by about 50% due to increased utilization by the fetus, increased renal clearance of iodide by about 30% to 50%, and increased binding to thyroid binding globulin (TBG). The fetus is solely dependent upon maternal thyroid hormone until midgestation and remains partially dependent on maternal thyroid hormone as maturation of the fetal thyroid system occurs late in the third trimester and postnatally. The fetus is totally dependent on the mother for its iodide supply

The Public Affairs Committee of the Neurobehavioral Teratology Society supports the recommendations of this paper, that all pregnant and lactating women should ingest a total of 250 micrograms of iodine daily and take daily supplementation of 150 micrograms to achieve this goal.

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throughout pregnancy (Glinoer, 2007). Thyroid hormones are necessary for normal fetal development. Moreover, studies have shown neurologic alterations and reduced IQ scores in children associated with mild to moderate hypothyroxinemia in the mother (Haddow et al., 1999; Costeira et al., 2011).

There is a negative feedback loop between serum thyroid hormone levels and pituitary production of thyroid stimulating hormone (TSH). High serum concentrations of thyroid hormones suppress pituitary production of TSH (thyrotrophin), and the identification of elevated TSH concentration in plasma is suggestive of hypothyroidism. A healthy, pregnant woman with inadequate iodine intake leading to overt hypothyroidism is at risk for pregnancy complications including preeclampsia, placental abruption, spontaneous abortion, preterm birth, and low birth weight (Casey et al., 2005; Krassas et al., 2010; Negro and Mestman, 2011).

United States population data indicate that 2% to 3% of healthy nonpregnant women have an elevated TSH (Allan et al., 2000; Casey et al., 2005; Stagnaro–Green et al., 2011). Of these women, 0.3% to 0.5% upon further testing are classified as overtly hypothyroid and 2% to 2.5% are classified as subclinically hypothyroid (Allan et al., 2000; Stagnaro–Green et al., 2011). Thyroid autoantibodies are detected in about 50% of pregnant women with subclinical hypothyroidism and in 80% of those women with clinical hypothyroidism. Iodine deficiency can cause hypothyroidism; although primarily a problem of the developing world, many developed nations have a degree of iodine deficiency (Stanbury et al., 1998).

It has been estimated that more than 2 billion people worldwide are at risk of iodine deficiency (Andersson et al., 2005) and some populations in the United States are marginally iodine deficient (Leung et al., 2011). The developing fetus and young child are particularly vulnerable because iodine is essential for normal development.

In the United States, iodine sufficiency is measured by the National Health and Nutrition Examination Survey (NHANES), an ongoing cross-sectional study representative of the U.S. population. NHANES III (1988–1994) reported that most populations in the United States are iodine sufficient; however, due to the higher glomerular filtration rate in pregnancy, urinary iodine concentration may not be an adequate measurement of iodine status in pregnancy (Soldin et al., 2003; Hollowell and Haddow, 2007). Taking pregnancy related factors into account, there is likely a small but meaningful percentage of women of reproductive age and pregnant women in the United States who are iodine deficient (Soldin et al., 2003; Hollowell and Haddow, 2007). In the 2007 to 2008 NHANES cohort, more than half of pregnant American women could be characterized as iodine insufficient based on urinary iodine concentration (Caldwell et al., 2011). About one in six pregnant women in this sample had moderate or severe deficiency. Moreover, in a recent report examining the association between hypertension, salt restriction, and iodine deficiency from the 2001 to 2004 NHANES, women restricting dietary salt had significantly lower urinary iodine concentrations and were more likely to be iodine deficient (Tayle and Jourdan, 2010).

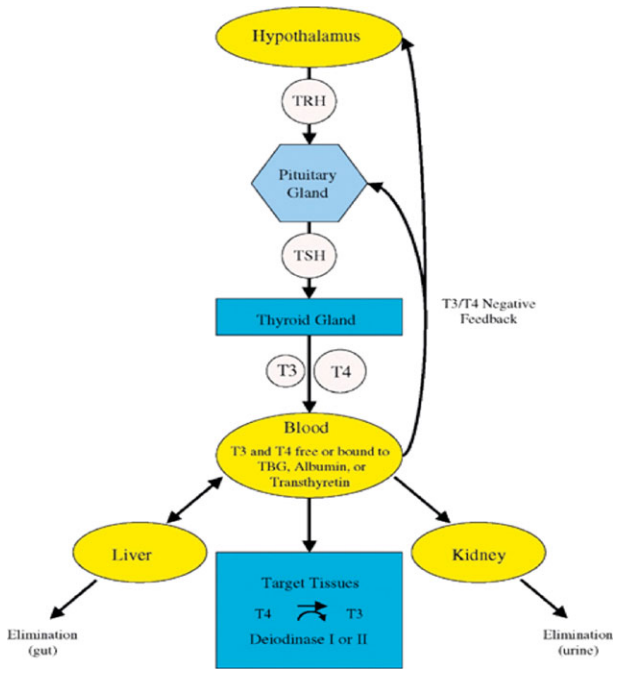

Figure 1. The thyroid system.

The Thyroid System

Thyroid hormones modulate lipid, carbohydrate, and protein metabolism and oxygen consumption by cells and are important for temperature regulation. In addition, thyroid hormones are essential for normal development of the nervous, cardiovascular, immune, and reproductive systems (Larsen and Ingbar, 1992). Thyroid hormones are produced and stored in the thyroid gland, located below the larynx in the neck. The principal thyroid hormones are T4 and T3 (Figure 1). Both hormones are released from the thyroid gland and are transported in the circulation bound primarily to TBG. Thyroid hormones may be released from the thyroid in its physiologically active form, T3, but about 80% of thyroid hormones are released into the circulation as T4 and converted to T3 by deiodinases in target tissues.

TSH is produced and released by the pituitary gland and stimulates the production and release of T3 and T4 from the thyroid gland. TSH is in turn produced in response to hypothalamic release of thyrotropin-releasing hormone. An increase in T3 or T4 blood concentrations inhibits the release of TSH from the pituitary gland and thyrotropin-releasing hormone from the hypothalamus. An underactive (hypothyroid) thyroid gland is associated with lower than normal circulating T3 and T4 levels and, if the pituitary and hypothalamus are intact, higher than normal TSH levels. A subcategory of hypothyroidism is subclinical hypothyroidism, defined by an elevated TSH level and normal levels of thyroid hormone.

Thyroid Function in Pregnancy

Pregnancy alters thyroid hormone metabolism and trimester-specific reference intervals are used for clinical thyroid testing (Table 1; Stagnaro–Green et al., 2011). Starting in the first trimester, increased circulating estro-

Table 1
Trimester Specific Reference Intervals for TSH

Nonpregnant	First trimester	Second trimester	Third trimester
0.4–4.0 mIU/L	0.1–2.5 mIU/L	0.2–3.0 mIU/L	0.3–3.0 mIU/L

Source: Adapted from the 2011 American Thyroid Association Clinical Guidelines (Stagnaro–Green et al., 2011).
TSH, thyroid stimulating hormone.

gen increases TBG by two to threefold. This increase in TBG results in elevated thyroid hormone binding and a decrease in free T4 and T3 in the circulation. In the presence of thyroid sufficiency, the decrease in free thyroid hormone levels is 10% to 15% (Nader, 2009). Human chorionic gonadotropin, which has TSH-like activity, increases during the first trimester. As a result, there is an increase in T3 and T4 and a proportional decrease in the pituitary production of TSH. Frequently, the TSH concentration is below its normal nonpregnant lower limit of 0.4 mIU/L, most notably between 8 and 14 postmenstrual weeks of pregnancy. Trimester-specific reference intervals for TSH (Table 1) have been recommended by the Endocrine Society and by the American Thyroid Association (ATA) (Stagnaro–Green et al., 2011).

The thyroid gland has the capacity to adapt to the changes of pregnancy as long as sufficient iodine is present. The decrease in free thyroid hormones increases TSH production and increases levels of thyroglobulin, a glycoprotein in the thyroid follicle important in the storage and synthesis of thyroid hormones. These changes can result in hypertrophy. Without sufficient iodine, the thyroid gland enlarges further to keep up with the demand for thyroid hormone production. An abnormally enlarged thyroid is called a goiter (Nader, 2009).

During pregnancy, maternal iodine requirements are increased to account for the needs of the developing fetus as well as increased maternal renal excretion (Marchioni et al., 2008; Nader, 2009). The ATA recommends daily iodine intake of 250 μg for both pregnant and lactating women, compared to 150 μg/day for nonpregnant adults (Table 2) (World Health Organization, 2001; Stagnaro–Green et al., 2011). However, chronic excessive iodine supplementation can block the production of thyroid hormones for several days (Wolff–Chaikoff effect). A study of pregnant Spanish women identified an association between elevated blood concentration of TSH, perhaps representing impaired thyroid function, and daily intake of iodine from supplements, as determined by questionnaire, of ≥200 μg (Rebagliato et al., 2010). There was no relationship, however, between TSH and spot urinary iodine concentration, which may be a more reliable indicator of iodine economy. Individuals are normally able to compensate for increased iodine intake by decreasing the active transport of iodine into the thyroid gland, which allows normal production. The ATA recommends that iodine intake not exceed 500 to 1100 μg/day during pregnancy due to concerns of fetal hypothyroidism (Stagnaro–Green et al., 2011). The World Health Organization recommends an upper limit of iodine intake of 500 μg/day.

Seaweed is the food with the highest iodine content; however, because seaweed is an organic source, the iodine content per serving is variable. Other sources of iodine include seafood, dairy products, eggs, and fortified grains (Table 3). Marine animals concentrate iodine from seawater (Institute of Medicine, Food, and Nutrition Board, 2001). In the United States, dairy products are an important source of dietary iodine, due to use of iodine in animal feed and in sanitizing products in the dairy industry (Office of Dietary Supplements [ODS], 2011). Iodine is present in fruits and vegetables in very low concentrations and varies depending on the soil and fertilizers used (Institute of Medicine, Food, and Nutrition Board, 2001). Some of the table salt available in the United States is iodized salt. The U.S. Food and Drug Administration recommends 46 to 76 mg of iodine per kilogram of salt. According to labels, all iodized salt contains 45 mg I/kg of salt. However, iodized salt samples examined were variable in iodine content and 47 of 88 iodized salt samples fell below the U.S. Food and Drug Administration recommended iodine content (Dasgupta et al., 2008).

A survey of prenatal multivitamins available in the United States showed that only 51% contained any iodine, and of those that did contain iodine, the iodine content varied greatly by brand (Leung et al., 2009).

Table 2
Dietary Iodine Requirements at Different Stages of Life

Group	Minimum iodine intake (μg/day)
Infants and children	90
Children 6–12 years of age	120
Adolescents and adults	150
Pregnant women	200 (250[a])
Lactating women	200 (250[a])

Sources: World Health Organization, 2001, and [a]Stagnaro–Green et al., 2011.

Table 3
Iodine μg/Serving in Some Common Foods

Food	μg/Serving	Percent daily value (nonpregnant adult[a])
Seaweed, sheet, 1 g	16–2984	11%–1989%
Cod, 3 ounces	99	66%
Yogurt, plain, low fat, 1 cup	75	50%
Iodized salt, 1.5 g	71	47%
Milk, reduced fat, 1 cup	56	37%
Fish sticks, 3 ounces	54	36%
Bread, white, enriched, 2 slices	45	30%
Shrimp, 3 ounces	35	23%
Egg	24	16%
Tuna, 3 ounces	17	11%
Cheese, cheddar, 1 ounces	12	8%
Raisin bran cereal, 1 cup	11	7%
Apple juice, 1 cup	7	5%
Banana	3	2%

Sources: Pennington et al., 1995; Teas et al., 2004; Office of Dietary Supplements, 2011.
[a]Recommended adult daily intake is 150 μg (100%) (Office of Dietary Supplements, 2011).

Table 4
Effects of Thyroid Deficiency in Humans

Maternal effects	Miscarriages, Anemia in Pregnancy, Preeclampsia, Abruptio Placenta
	Post-Partum Hemorrhage
Fetus (from effects of maternal hypothyroidism)	Abortion, stillbirth
	Increased perinatal mortality
	Increased infant mortality
	Neurologic cretinism: mental deficiency, deaf mutism, spastic diplegia
	Myxedematous cretinism: mental deficiency, hypothyroidism and dwarfism
	Psychomotor defects
	Neonatal goiter
	Neonatal hypothyroidism
	Premature birth
	Low birth weight
	Increased neonatal respiratory distress
Child and adolescent	Impaired mental and physical functioning
Adult	Goiter
	Impaired mental functioning
	Iodine-induced hyperthyroidism
All ages	Goiter
	Hypothyroidism
	Impaired mental function
	Increased susceptibility to thyroid cancer from nuclear radiation exposure

Sources: Hetzel et al., 1983; Stanbury et al., 1998; Delange et al., 1999.

Reproductive Consequences in Women

Clinical hypothyroidism has been associated with increased risk of poor perinatal outcome including prematurity, low birth weight, miscarriage, preeclampsia, fetal death, and impaired fetal neurocognitive development (Table 4). A cohort study reported an 8.1% rate of fetal death in pregnant women with TSH >10 mIU/L compared to 0.9% in controls ($p < .001$) (Allan et al., 2000). More women who had a miscarriage or fetal loss had an increase in TSH levels above the 97.5 percentile compared to women with normal pregnancies (5.9% vs 2.5%; $p < .05$) and free T4 levels below the 2.5 percentile (5.0% vs 2.5%; $p < .05$) (Ashoor et al., 2010).

Subclinical hypothyroidism is also associated with poor pregnancy outcomes and potential fetal neurocognitive deficits, but the data are more variable than those for clinical hypothyroidism. Clinically, the severity of subclinical hypothyroidism is determined by the TSH level as well as the presence or absence of thyroid peroxidase antibody (TPOAb). Thyroid peroxidase is an enzyme made in the thyroid gland that is important in the production of thyroid hormone. Subclinical hypothyroid antithyroid peroxidase antibody positive (TPOAb+) women were at higher risk of pregnancy complications and there was a higher miscarriage rate in TPOAb- patients when TSH was above 2.5 mIU/L (Negro et al., 2010a). In contrast, analysis of several cohorts reported no adverse outcomes from subclinical maternal hypothyroidism (Cleary–Goldman et al., 2008; Männistö et al., 2009).

The most detrimental effect of maternal iodine deficiency is on the developing fetal brain. Thyroid hormone is important in the myelination of the central nervous system, which occurs most notably during perinatal and postnatal fetal development. The most marked neurocognitive effect seen in severe cases of maternal hypothyroidism is ''cretinism'' of the offspring. This is characterized by mental retardation, dwarfed stature, bone dystrophy, and a low basal metabolism. An iodine-deficient diet in the pregnant woman has been strongly linked to mental retardation in her offspring. A meta-analysis of 18 studies concluded that maternal iodine deficiency lowered offspring IQ score by 13 points (Bleichrodt and Born, 1994). Mild maternal hypothyroidism during pregnancy has also been associated with a decrease of 4 IQ points in the offspring (Haddow et al., 1999). Li et al. (2010) also noted a decrease in IQ in the offspring of hypothyroid and hypothyroxinemic mothers as well as in those with normal thyroid function but positive thyroid antibodies.

There is strong evidence that iodine supplementation improves fetal outcomes with severe iodine deficiency (Zimmermann, 2011). Women supplemented before conception or early in pregnancy have reduced neonatal mortality and their children have improved IQ scores and fewer neurologic abnormalities when compared with control groups (Cao et al., 1994; O'Donnell et al., 2002). Neurobehavioral outcomes in children from areas with mild to moderate iodine deficiencies also improved with supplementation in early pregnancy (Berbel et al., 2007; Berbel et al., 2009). However, for women with mild iodine deficiency, data on iodine supplementation and fetal outcomes are more limited (Zimmermann, 2007).

Treatment of Maternal Hypothyroidism

To date, no prospective randomized studies have been conducted to evaluate the effectiveness of treatment of hypothyroidism in pregnant women with respect to neonatal outcomes. Randomized studies of the treatment of subclinical hypothyroidism have been inconclusive (Lazarus. 2010). Nonrandomized studies confirm the benefit of treating hypothyroidism during pregnancy (Haddow et al., 1999).

One prospective trial indicated that thyroid antibodies are also involved because treatment with thyroxine of women who are subclinically hypothyroid and have TPOAb+ leads to improved obstetrical outcome (Negro et al., 2010b). Treatment of women who were subclinically hypothyroid and TPOAb+ decreased the risk of at least one of the following obstetrical outcomes: miscarriage, hypertensive disorders, gestational diabetes, placental abruption, cesarean delivery, congestive heart failure, preterm labor, respiratory distress, neonatal intensive care unit admission, aberrant birth weights, preterm delivery, low Apgar score, or perinatal death.

Public Health Initiatives

Urinary iodine excretion is a reflection of dietary iodine intake, because 90% of all iodine is renally excreted (Patrick, 2008). One-time spot urinary analysis is normally used for iodine assessment of a population iodine intake, but 24-hour urine collections or multiple spot

urines are considered more accurate as there is considerable diurnal and day to day variation in iodine excretion. Iodine supplementation and universal salt iodination have been integral methods in managing iodine deficiency, which affects one third of the global population (Andersson et al., 2005). In 1993, there were 110 countries that had iodine deficiency as a national public health problem versus 47 countries in 2007 (Andersson et al., 2010).

Recommendations

Pregnant and lactating women require additional iodine intake whether they live in iodine-sufficient or iodine-deficient areas. The ATA recommends that women receive 250 micrograms iodine intake daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150 micrograms of iodine (Public Health Committee of the American Thyroid Association et al., 2006; Stagnaro–Green et al., 2011). We concur with this recommendation. Iodine supplementation should begin by 4 to 6 menstrual weeks of pregnancy to ensure adequate maternal levels of thyroid hormone for fetal brain development. Supplementation of the mother should continue through lactation, because breastfeeding is the only source of iodine nutrition in breastfed infants. Iodine supplementation should be in the form of potassium iodide, which will provide the most stable delivery.

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