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Iodine Nutrition in Pregnancy and Lactation

Angela M. Leung, MD, MSc, Elizabeth N. Pearce, MD, MSc*, and **Lewis E. Braverman, MD**
Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, MA, USA

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IODINE PHYSIOLOGY DURING PREGNANCY

Beginning in early gestation, maternal thyroid hormone production normally increases by approximately 50% in response to increased levels of serum thyroxine-binding globulin (resulting from the increase in estrogen levels) and because of stimulation of thyrotropin (TSH) receptors by human chorionic gonadotropin.¹ The placenta is a rich source of the type 3 inner ring deiodinase, which enhances the degradation of thyroxine (T₄) to bioinactive reverse triiodothyronine (T₃).² Thus, thyroid hormone demand increases, which requires an adequate iodine supply that is obtained primarily from the diet and/or as supplemental iodine (Fig. 1). In addition, fetal thyroid hormone production increases during the second half of pregnancy, further contributing to increased maternal iodine requirements because iodide readily crosses the placenta.

After oral ingestion, iodide is rapidly absorbed through the stomach and duodenum.³ Iodide, in its pure form, is 100% bioavailable and fully absorbed. Plasma inorganic iodide is then transported through the circulation to be either taken up by the thyroid in varying amounts (5%–100% of absorbed iodine), depending on the iodine supply and the functional state of the thyroid,³ or it is renally excreted. The normal thyroid gland contains approximately 15 g of iodine.⁴ The inability to compensate for the increased iodine demand of pregnancy is associated with the development of maternal goiter due to TSH stimulation.⁵

The primary route of iodine excretion is through the kidney,⁶ which accounts for more than 90% of ingested iodine.³ Beginning in early pregnancy, the glomerular filtration rate of iodide increases by 30% to 50%,¹ thereby further decreasing the circulating pool of plasma iodine.⁷ Stilwell and colleagues⁸ reported that median urinary iodine levels in Tasmania, a region of mild iodine deficiency, decline after the elevated excretion seen in early pregnancy. A comparison of pregnant women from various countries demonstrated that peak

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*Corresponding author. Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, 88 East Newton Street, Evans 201, Boston, MA 02118. elizabeth.pearce@bmc.org.

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gestational urinary iodine levels vary, thus suggesting differences in renal excretion thresholds by regional dietary iodine intake.⁹

Because of increased thyroid hormone production, increased renal iodine losses, and fetal iodine requirements in pregnancy, dietary iodine requirements are higher in pregnant adults than in nonpregnant adults.¹⁰ Guidelines for daily dietary iodine intake of pregnant women, based on several studies that assessed the effect of iodine supplementation on maternal thyroid volume,¹¹ indicate a higher iodine requirement in these women than that for nonpregnant nonlactating adolescents and adults (Table 1).

METHODS TO ASSESS IODINE SUFFICIENCY

There are several accepted methods used in the monitoring of population iodine sufficiency.¹¹ Median spot urinary iodine concentrations (as a biomarker for dietary iodine intake)¹² reflect iodine intake over the recent few days. Thresholds for median urinary iodine sufficiency have been identified for populations but not for individuals, given significant day-to-day variation of iodine intake.¹³ As shown in Table 2, population iodine sufficiency is defined by median urinary iodine concentrations of 100 µg/L or more in nonpregnant women and children younger than 2 years and 150 µg/L or more in pregnant women.¹⁴

Serum levels of TSH and thyroglobulin increase over weeks to months of iodine deficiency, although these concentrations often remain in the normal range and are thus not a good measure of mild iodine deficiency. The World Health Organization (WHO) guideline of using the upper limit (3%) of neonatal TSH values of more than 5 mIU/L has been regarded as one method to define population iodine sufficiency, although it has been suggested to be unreliable.¹⁵ Goiter size, assessed by palpation or ultrasonography, is used to assess long-term iodine sufficiency. The WHO has established international reference ranges for serum thyroglobulin and thyroid gland volumes to be used in the monitoring of iodine deficiency in school-aged children.^{16,17}

IMPORTANCE OF ADEQUATE IODINE NUTRITION

Consequences of iodine deficiency include endemic goiter, cretinism, intellectual impairments, growth retardation, neonatal hypothyroidism, and increased pregnancy loss and infant mortality,¹⁸ many of which were recognized beginning in the 1970s by Pharoah and colleagues¹⁹ in Papua New Guinea. Research since then has shown that thyroid hormone plays a particularly vital role in fetal and infant neurodevelopment in utero and in early life because it is required for oligodendrocyte differentiation and myelin distribution.²⁰ Animal studies have demonstrated that low levels of thyroid hormone in early pregnancy up to midgestation, when the developing fetus is completely reliant on maternal thyroid hormone stores, impair radial migration of neurons to the cortex and hippocampus and result in behavior changes.²¹

Insufficient iodine levels during pregnancy and the immediate postpartum period result in neurologic and psychological deficits in children.^{22,23} The prevalence of attention deficit and hyperactivity disorders is higher in the offspring of women living in iodine-deficient areas than those in iodine-replete regions.²⁴ Intelligence quotient (IQ) levels of children living in severely iodine-deficient areas are an average of 12.45 points lower than those living in iodine-sufficient areas and are improved with iodine supplementation.²⁵ In Spain, a region of mild iodine deficiency, children with urinary iodine levels more than 100 µg/L have significantly higher IQ levels than those with urinary iodine levels less than this threshold.²⁶ Although public health efforts have improved iodine nutrition over the past few

decades, iodine deficiency affects more than 2.2 billion individuals (38% of the world's population)²⁷ and remains the leading cause of preventable mental retardation worldwide.¹⁴

IODINE SUPPLEMENTATION DURING PREGNANCY

Many studies have established the benefits of iodine supplementation during pregnancy in areas of severe iodine deficiency.²⁸ One of the earliest studies was a randomized controlled trial during the early 1970s in Papua New Guinea, in which pregnant women living in the remote highlands were administered injections of Lipiodol, a solution of iodinated poppy seed oil, and found to have decreased rates of fetal death and endemic cretinism for up to 5 years compared with untreated women.¹⁹

There have been 6 controlled trials to assess the effects of iodine supplementation during pregnancy in several moderately iodine-deficient European regions. In Italy, 18 iodine-untreated women had larger thyroid volumes than 17 women who received 120 to 180 µg/d of iodine beginning during the first trimester.²⁹ Investigators in Denmark reported that iodine-treated women have decreased maternal TSH levels compared with women who received no supplementation.^{30,31} Among 180 pregnant women in Belgium, the infants of those who received 100 µg/d potassium iodide had decreased thyroid volumes.³² Liesenkotter and colleagues³³ reported similar findings among the infants of 38 pregnant women in Germany who received 300 µg/d potassium iodide starting at 10 to 12 weeks' gestation. In contrast, Antonangeli and colleagues³⁴ reported that there were no differences in maternal thyroid function or thyroid gland size between 86 iodine-supplemented and iodine-unsupplemented women.

In a mildly iodine-deficient area of Italy, consumption of iodized salt in the 24 months preceding pregnancy, compared with initiation of iodized salt ingestion on becoming pregnant, decreased the risk of maternal thyroid dysfunction in women with negative thyroid antibody titers.³⁵ In the only 2 studies of iodine supplementation in mildly and moderately iodine-deficient women evaluating neurobehavioral outcomes, infants born to mothers who received iodine during pregnancy had improved psychological and neurocognitive measures compared with those born to nonsupplemented mothers. Berbel and colleagues³⁶ reported that children of women who were both mildly hypothyroxinemic from a mildly iodine-deficient region and supplemented with 200 µg potassium iodide per day beginning at 12 to 14 gestational weeks compared with women who received no supplementation had delayed neurocognitive performance at 18 months of age compared with children of women who received supplementation at 4 to 6 gestational weeks. Similarly, Velasco and colleagues³⁷ found that infants aged 3 to 18 months of mildly iodine-deficient mothers who received 300 µg potassium iodide per day during the first trimester had higher neuropsychological assessment scores than those of mothers who received no iodine supplementation.

CONSEQUENCES OF HYPOTHYROIDISM IN PREGNANCY

Maternal hypothyroidism, as characterized by elevated TSH levels, occurs in an estimated 2.5% of all pregnancies in the United States.³⁸ The fetal thyroid does not begin to concentrate iodine until 10 to 12 weeks of gestation and is not controlled by fetal pituitary TSH until approximately 20 weeks of gestation.³⁹ Before this, the fetus is reliant on maternal T₄ that crosses the placenta in very small quantities.⁴⁰

Because thyroid hormone is required for normal neurodevelopment,⁴¹ even mildly low maternal T₄ and/or elevated maternal serum TSH levels during pregnancy may result in cognitive delays in the offspring. Haddow and colleagues⁴² reported that 7- to 9-year-old children whose pregnant mothers had untreated mild hypothyroidism have an average of 7 IQ points lower than those of matched euthyroid control mothers. Subclinical

hypothyroidism and low free T₄ concentrations in women during pregnancy are independent predictors of impaired neurodevelopment in their children.⁴³⁻⁴⁷ The most recent study supporting these data was the Dutch Generation R study of 3659 women and their infants, in which severe maternal hypothyroxinemia was associated with both expressive language delay and nonverbal cognitive delay in their infants at 30 months.⁴⁷

IODINE PHYSIOLOGY DURING LACTATION

Thyroidal iodine turnover rate is more rapid in infants.¹¹ Thus, adequate breast milk iodine levels are particularly important for proper neurodevelopment in nursing infants. Iodine is secreted into breast milk at a concentration gradient 20 to 50 times that of plasma⁴⁸ through increased expression of the sodium/iodide symporter (NIS) present on lactating breast cells.⁴⁹ In iodine-sufficient areas, breast milk iodine concentrations are generally adequate to meet infants' iodine nutritional needs based on iodine balance studies.⁵⁰ Even compensatory mechanisms may not be adequate to meet the increased demands for thyroid hormone production and iodine intake for mothers living in iodine-deficient areas. In a recent study, the iodine needs for breastfed infants in iodine-deficient New Zealand remained inadequate even when their mothers were supplemented with 150 µg/d of iodine during the first 6 postpartum months.⁵¹

IODINE NUTRITION IN LACTATION

Because breastfed infants are reliant on maternal dietary iodine intake, recommendations for dietary iodine intake during lactation range from 250 to 290 µg/d, higher than the 150 µg/d recommended for nonpregnant and nonlactating adolescents and adults (see Table 1). These thresholds were determined based on a mean breast milk iodine concentration of 146 µg/L, as was measured in 37 women in the United States,⁵² and the assumption that infants ingest an average of 0.78 L/d of breast milk during 0 to 6 months and 0.60 L/d during 6 to 12 months.⁵³

Data regarding breast milk iodine levels in lactating women in the United States are extremely limited. Small studies (57 women in the largest sample)⁵⁴ have demonstrated that median breast milk iodine levels in women in the United States range from 35 to 155 µg/L.^{52,54-57} Furthermore, breast milk iodine levels vary temporally, as was reported by Kirk and colleagues⁵⁶ in a study of 10 lactating women in the United States. Among 108 total samples, there was considerable variation of breast milk iodide levels (which comprises 89%–90% of breast milk iodine [S. Pino, BS, unpublished data, 2004]) within and between individuals over a 3-day period. Larger studies are needed to determine the iodine sufficiency of lactating women in the United States and their breastfed infants.

IODINE NUTRITION IN THE UNITED STATES

Since the 1920s, dietary iodine in the United States has been considered adequate. However, sources of iodine in the US diet have been difficult to identify because there are a wide variety of potential sources and a wide variation in the iodine content of some common foods and food iodine content is not listed on packaging. In the United States, population iodine deficiency has been eliminated by means of silent prophylaxis. Sources of dietary iodine include iodized salt (due to the addition of iodine to table salt as a public health measure), dairy foods (due to the iodophor cleansers of milk cans and teats), and bread dough (due to the use of iodate as bread conditioners in some bakeries).⁵⁸

Results of the Total Diet Studies by the US Food and Drug Administration (FDA) have demonstrated that iodine is found mostly in grain products, milk, and cheese in the United States.⁵⁹ Most foods contain 3 to 75 µg of iodine per serving.⁵³ Based on the most recent US

FDA's Total Diet Study, the estimated average daily iodine intake ranges from 138 to 353 µg per person.⁶⁰ A survey of more than 700 schoolchildren in the United States during the early 1970s using diet frequency diaries and urinary iodine levels found that milk, iodized salt, and iodated bread were the primary sources of iodine intake.⁶¹ In addition, sources of iodine exposure may include use of iodine-rich medications (such as amiodarone), topical antiseptics, multivitamins, radiographic contrast agents, and water purification tablets.

According to data from the National Health and Nutrition Examination Survey (NHANES), the median urinary iodine concentration in adults in the United States decreased by more than 50% from the early 1970s to the late 1990s (Fig. 2).⁶² Of particular concern in the NHANES data is that the prevalence of urinary iodine values less than 50 µg/L among women of childbearing age increased by almost 4-fold, from 4% to 15%, during this period. The most recent NHANES survey (2005–2008) demonstrated that 35.3% of pregnant women had urinary iodine levels less than 100 µg/L,⁶³ which suggests mild iodine sufficiency.¹⁴ Reductions in the US dietary iodine level have been variously ascribed to a possible reduction in the iodine content of dairy products, the removal of iodate dough conditioners in commercially produced bread, new recommendations for reduced salt intake for blood pressure control, and the increasing use of noniodized salt in manufactured or premade convenience foods.⁶⁴

A study of aggregate NHANES data from 2001 to 2006 showed that the included pregnant women in the United States were marginally iodine sufficient (N = 326; median urinary iodine = 153 µg/L) and lactating (N = 53; median urinary iodine = 115 µg/L) and nonpregnant nonlactating women (N = 1,437; median urinary iodine = 130 µg/L) were both iodine deficient.⁶⁰ We reported that the median urinary iodine concentration of a sample of 100 women in the Boston area in their first or second trimesters of pregnancy was 149 µg/L, including 9% with values less than 50 µg/L.⁶⁵

PUBLIC HEALTH EFFORTS OF IODINE SUPPLEMENTATION

A public health approach to iodine supplementation in the United States has been advocated. The American Thyroid Association has recommended that women in North America receive dietary supplements containing 150 µg of iodine daily during pregnancy and lactation and that all prenatal vitamins contain 150 µg of iodine.⁶⁶ These recommendations have not yet been widely adopted. Only 20.3% of pregnant and 14.5% of lactating women in the United States take a supplement containing iodine, according to the NHANES data.⁶⁷ At present, 114 of 223 (51%) brands of prescription and nonprescription prenatal multivitamins marketed in the United States list iodine as a constituent, and many of those which contain iodine do not contain the labeled amount, especially when kelp is the iodine source.⁶⁸ The US Women, Infants, and Children Nutrition Program has recommended that all prenatal multivitamins administrated to women in its program contain 150 µg of iodine per daily serving beginning in 2010.

The major concerns regarding the global burden of iodine deficiency are related to goiter; neurocognitive impairments; and, in severe deficiency, hypothyroidism resulting in cretinism. In 1990, the United Nations World Summit for Children set forth the goal of eliminating iodine deficiency worldwide,⁶⁹ and considerable progress has since been achieved. This goal has largely been led by programs of universal salt iodization in various countries, in line with the recommendations by the WHO and the International Council for the Control of Iodine Deficiency Disorders^{27,70} and use of oral potassium iodide drops or intramuscular iodized oil injections. Median urinary iodine concentrations of infants residing in iodine-sufficient countries range from 90 to 170 µg/L, which suggests optimal iodine nutrition by criteria as defined by the WHO.¹⁴ Although these efforts have been successful

in many countries, the WHO estimates that 2 billion people, including 285 million school-aged children, remain iodine deficient.⁷¹

The WHO has proposed that an iodine intake of 500 µg/d poses no excessive risk,¹⁴ and the European Food Safety Agency and the US Institute of Medicine have recommended 600 µg/d and 1100 µg/d, respectively, as the tolerable upper limit for iodine per day.^{53,72} Thus, although the overall US adult population remains iodine sufficient by WHO standards, a subset of pregnant and lactating women may have inadequate dietary iodine intake.

SUBSTANCES INTERFERING WITH IODINE USE

Competitive inhibitors of NIS, such as perchlorate, thiocyanate, and nitrate, can decrease the entry of iodine into the thyroid and lactating breast, thereby potentially exacerbating the effects of dietary iodine insufficiency. Low-level perchlorate exposure seems to be ubiquitous in the US, European, and South American population. Environmental perchlorate comes from a variety of sources, is extremely stable as an inorganic salt, and persists in low levels in soil and groundwater over long periods.⁷³ In the United States, perchlorate has been found in many substances, including tobacco, alfalfa, tomato, cow's milk,⁵⁵ cucumber, lettuce, soybeans, eggs, and multivitamins (including prenatal multivitamins).⁷⁴ Following the development of sensitive detection methods, perchlorate has been measured in the drinking water of communities around the United States.

When given in pharmacologic doses, perchlorate decreases the active transport of iodine into the thyroid and possibly breast milk by competitively inhibiting the NIS with 30 times its affinity for iodide.⁷⁵ Furthermore, recent studies in lactating mice have suggested that perchlorate is actively transported into breast milk,⁷⁶ thus potentially decreasing infants' thyroidal iodine uptake. In the NHANES 2001 to 2002 survey, perchlorate was detected in all 2820 spot urine samples (median urine perchlorate concentration, 3.6 µg/L) and was a significant negative predictor of total T₄ values and a positive predictor of TSH values in women, primarily those with urine iodine concentrations less than 100 µg/L.^{77,78} However, these relationships were not seen in men,⁷⁸ a follow-up subset analysis of this dataset (which analyzed only women of childbearing age) using creatinine-adjusted urinary iodine values,⁷⁹ or a large European study assessing serum thyroid function tests of iodine-deficient pregnant women.⁸⁰ Recently, the US FDA reported in a Total Diet Study that infants and children have the highest estimated intakes of perchlorate by body weight.⁸¹

There are limited data regarding breast milk iodine⁸² and perchlorate concentrations in women in the United States. We reported that the median breast milk iodine concentration in 57 women in Boston area was 155 µg/L,⁵⁴ similar to that of a 1984 study of 37 women (178 µg/L).⁵² However, the median breast milk iodine levels in our study were far higher than those (33.5, 43.0, and 55.2 µg/L) observed recently by Kirk and colleagues^{55,56} in 3 studies.⁵⁷ Kirk and colleagues⁵⁵ also measured perchlorate levels in the breast milk of 36 women from 18 states and found detectable levels in all the samples (range, 0.6–2.2 µg/L). Breast milk iodide and perchlorate levels were inversely correlated in the 6 samples with perchlorate concentrations of at least 10 µg/L, although there were no correlations between breast milk iodide and perchlorate in the full data set.⁵⁵ We reported no correlation between breast milk and colostrum iodine and perchlorate concentrations, even in those breast milk samples with perchlorate concentrations of 10 µg/L or more.^{54,83}

Similarly, exposures to thiocyanate, a metabolite of cyanide that is produced as a byproduct of cigarette smoke, and nitrate, which is produced naturally and is present in many prepared foods, are able to decrease NIS activity, thereby decreasing iodine availability. Naturally goitrogenic foods include those that contain cyanogenic glucosides (which become metabolized to thiocyanate), such as cassava, millet, maize, sweet potatoes, lima beans, and

cruciferous vegetables (which contain thiocyanates and isothiocyanates), such as cabbage, Brussels sprouts, cauliflower, broccoli, and horseradish.¹⁸ However, the thiocyanate content of these foods is low, and their ingestion does not usually produce clinically significant sequelae unless severe iodine deficiency is present.

One recent study in Denmark concluded that cigarette smoking decreases breast milk iodine concentrations,⁸⁴ and we demonstrated the same effect in a small cohort of lactating women in Boston area.⁵⁴ Comparatively, perchlorate is a potent inhibitor of NIS; its effects are 15-fold greater than thiocyanate, 30-fold compared with iodide, and 240-fold compared with nitrate.⁷⁵ Nonetheless, because exposure to thiocyanate and nitrate is ubiquitous, the additive effects on iodide uptake may be important when assessing iodine availability.

The urinary levels of selenium and iodine in pregnant women are closely correlated.⁸⁵ Selenium is an important component of glutathione peroxidase and selenoproteins, which include the 3 thyroid hormone deiodinases. Thus, insufficient selenium may result in the accumulation of damaging peroxides in the thyroid and impair the peripheral deiodination process required to generate the active thyroid hormone, T₃, from T₄. Although selenium nutrition is generally adequate in humans, rare conditions resulting in selenium deficiency may be important in the pathogenesis of hypothyroidism.⁸⁶ A recent study by Negro and colleagues⁸⁷ reported that selenium supplementation of 200 µg/d during pregnancy and in the postpartum period reduced the prevalence of permanent maternal hypothyroidism (11.7%) compared with women who did not receive supplementation (20.3%) ($P<.01$). The findings of this study are very preliminary, and currently there are no recommendations for selenium supplementation during pregnancy and lactation.

SUMMARY

Adequate iodine nutrition during pregnancy and lactation is needed for thyroid hormone synthesis and normal neurodevelopment of the developing fetus in utero and in the breastfed infant. Iodine deficiency during pregnancy has been associated with impairments of infant neurologic and psychological outcomes. Studies of maternal iodine supplementation in severe iodine deficiency have demonstrated reductions in the rates of fetal death and endemic cretinism. Iodine supplementation in areas of moderate iodine deficiency has shown decreased maternal thyroid volumes and TSH levels and, in areas of mild iodine deficiency, improvements in infants' neurocognitive measures.

Although the overall adult population in the United States remains iodine sufficient in recent national surveys, a subset of pregnant and lactating women may have inadequate dietary iodine intake. A public health approach has been undertaken to achieve recommended median urinary iodine concentrations during pregnancy and lactation. Recent guidelines have recommended that women in the United States take a multivitamin containing 150 µg of iodine during pregnancy and lactation. Further studies are needed to assess the impact of environmental exposures to substances that may interfere with iodine use.

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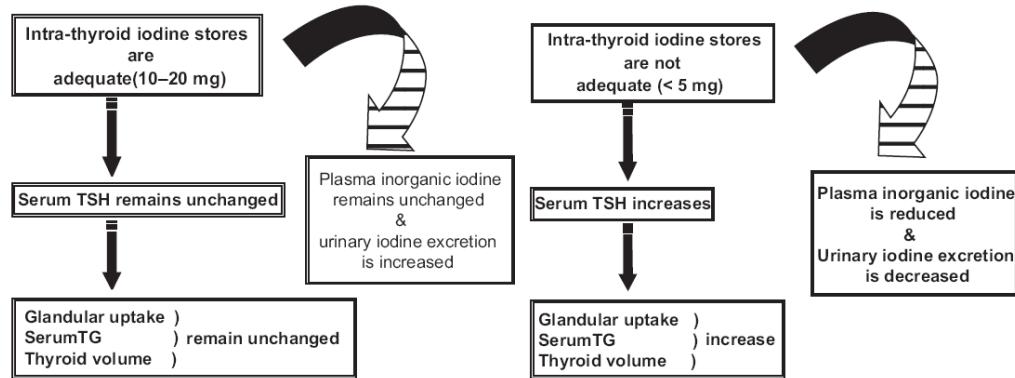
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**Fig. 1.**

Conceptual models of adequate (*left panel*) and inadequate (*right panel*) iodine nutrition and thyroid function. (*Adapted from* Glinoer D. The importance of iodine nutrition during pregnancy. *Public Health Nutr* 2007;10(12A):1543; with permission.)

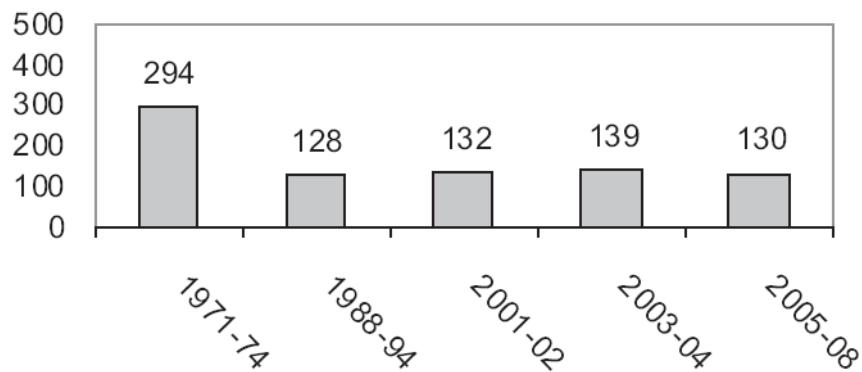


Fig. 2.
US dietary iodine in women of childbearing age: NHANES data from 1971 to 2008. (Data from Refs.^{62,63,88,89})

Table 1

Guidelines for daily dietary iodine intake

Institute	Nonpregnant Nonlactating Adolescents and Adults (μ g)	Pregnant Women (μ g)	Lactating Women (μ g)
Institute of Medicine ⁴⁸	150	220	290
WHO, UNICEF, ICCIDD ¹⁵	150	250	250
Endocrine Society ⁸⁹	—	250	250

Table 2

Thresholds for population iodine sufficiency based on median urinary iodine concentrations

	Pregnancy ($\mu\text{g/L}$)	Lactation ($\mu\text{g/L}$)	Children Younger Than 2 Y ($\mu\text{g/L}$)
Insufficient	<150	<100	<100
Adequate	≥ 150	≥ 100	≥ 100

Data from Li M, Eastman CJ. Neonatal TSH screening: is it a sensitive and reliable tool for monitoring iodine status in populations? Best Pract Res Clin Endocrinol Metab 2010;24(1):63–75.