Review Article

Iodine and Pregnancy

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Iodine is a necessary element for the production of thyroid hormone. We will review the impact of dietary iodine status on thyroid function in pregnancy. We will discuss iodine metabolism, homeostasis, and nutritional recommendations for pregnancy. We will also discuss the possible effects of environmental contaminants on iodine utilization in pregnant women.

1. Iodine Homeostasis in Pregnancy

1.1. Iodine Absorption and Metabolism. Iodine, consumed in food, water, or supplements, is absorbed by the stomach and duodenum (97%) [1]. Its only known use in the human body is in the production of thyroid hormone. Uptake of iodine by the thyroid varies with intake. When iodine intake is sufficient, the proportion cleared from the blood by the thyroid ranges from 10% to 80% of absorbed iodine [1]. The active transport of iodine from the blood into the thyroid is regulated by thyroid-stimulating hormone (TSH) from the pituitary gland and by the concentration of iodine in the blood. This active transport is mediated by the sodium-iodine symporter (NIS), a protein present on the basolateral surface of the thyroid epithelial cell [1]. Iodine entering the thyroid is oxidized to form "active" iodine which then iodinates tyrosine to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of MIT and DIT through an ether linkage generates the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), which are then cleaved from thyroglobulin, pass through the golgi, and are secreted into the peripheral circulation. All of the steps directed toward the generation of T4 and T3 are stimulated by thyroid peroxidase (TPO) (Figure 1). The half-lives of T4 and T3 in the circulation are approximately one day for T3 and seven days for T4. Peripheral deiodinases further metabolize thyroid hormone and add to circulating iodine (Figure 2). In particular, deiodinase 2 (D2) is responsible for the majority of extrathyroidal T3 production by cleaving iodide from the 5^1 position. The iodine that is cleaved from T4 and T3 re-enters the circulation where it is available for reutilization by the thyroid. Iodine that is not actively transported into the thyroid is primarily excreted in the urine (90%) with a very small amount present in the feces [1].

1.2. Physiologic Changes in Pregnancy. Pregnancy induces several major changes to thyroid physiology. The first is increased demand on the maternal thyroid gland. T4 production increases approximately 50% starting in early pregnancy. High levels of circulating estrogen during pregnancy decrease catabolism of the sialic acid-rich thyroxine-binding globulin (TBG) [2]. Consequently, circulating TBG levels increase 1.5-fold, increasing the levels of circulating total T3 and T4 and requiring an increase in thyroid hormone production to maintain normal unbound thyroid hormone levels. Additionally, in early gestation, the thyroid is stimulated not only by TSH but by the alpha subunit of human chorionic gonadotropin (hCG), which also binds to and stimulates the TSH receptor [3]. hCG is produced by the syncytiotrophoblasts of the developing pregnancy. Its production begins in the first days of pregnancy and peaks at 9–11 weeks of gestational age. Levels then decline until approximately 20 weeks of gestation and remain stable for the remainder of the pregnancy [3]. Finally, the placenta is
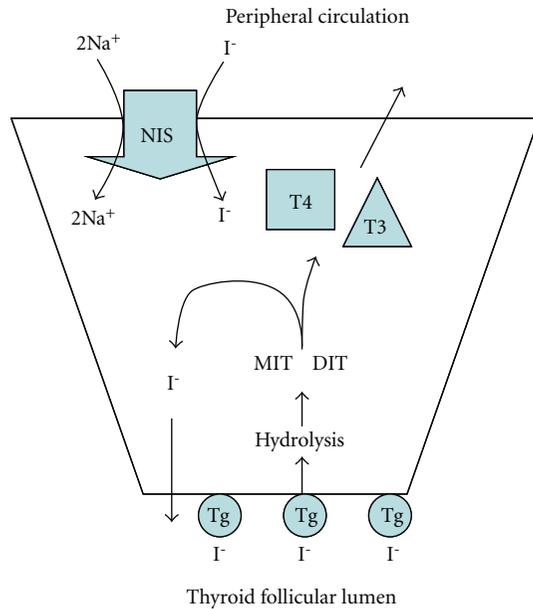
Figure 1: Thyroid hormone synthesis. NIS: Sodium-iodide symporter; T4: Thyroxine; T3: Triiodothyronine; MIT: Monoiodothyronine; DIT: Diiodothyronine; Tg: Thyroglobulin (I^-: iodinated).

an active site for the inner ring deiodination of T4 and T3, generating the inactive iodothyronines, reverse T3 and 3, 3^1-T2, respectively, presumably as a means of modulating the amount of active hormone that passes to the fetus [4]. (Figure 2) These processes all contribute to the increase in thyroid hormone requirement during pregnancy.

Increased thyroid hormone production in pregnancy requires adequate iodine availability. In iodine-replete regions, women typically begin pregnancy with 10–20 mg of iodine stored in the thyroid and, with continued sufficient iodine ingestion, are able to meet the increased demands of pregnancy. However, urinary iodine concentration (UIC), a reflection of iodine status, declines across pregnancy in women from iodine-deficient regions who may begin pregnancy with inadequate intrathyroidal iodine stores which are rapidly depleted [2]. If adequate iodine is not available, TSH rises and consequently goiter develops [2].

Another reason for increased iodine requirements in pregnancy is the increase in maternal glomerular filtration rate. Because iodine is passively excreted, increased renal glomerular filtration results in increased losses of ingested iodine [5].

The fetus and placenta also consume a proportion of maternal thyroid hormone and iodine. Fetal thyroidogenesis occurs by approximately the twelfth week of gestation. The fetal thyroid is capable of organifying iodine by approximately the 20th week of gestation. Before this time, maternal T4—the only form of thyroid hormone that can traverse the placenta in small amounts—must be adequate to meet the metabolic needs of the fetus. Fetal deiodinase converts maternal T4 to the bioactive T3 [6]. Once fetal thyroid gland function is established, fetal thyroidal turnover of iodine is much higher than adult [7]. Therefore, the fetal iodine

store—supported exclusively by maternal intake—must be continuously refreshed.

Iodine homeostasis varies across the three trimesters as metabolic needs fluctuate. After parturition, maternal iodine continues to be the only source of iodine to the breast-fed neonate. NIS is present in breast tissue and is responsible for concentrating iodine in colostrum and breast milk [8].

2. Effects of Iodine Deficiency

2.1. Effects of Severe Iodine Deficiency. Severe dietary maternal iodine deficiency in pregnancy has the potential to cause both maternal and fetal hypothyroidism. Severe iodine deficiency is associated with poor obstetric outcomes including spontaneous abortion, prematurity, and stillbirth [9]. Thyroid hormone plays an essential role in neuronal migration, myelination, and synaptic transmission and plasticity [6, 10]. Animal models have demonstrated that even mild and transient maternal hypothyroxinemia during pregnancy can disrupt neuronal migration in the fetus, resulting in ectopic neurons in different cortical layers including the subcortical white matter and hippocampus [11]. Therefore, iodine deficiency is associated with adverse effects on the fetus including congenital anomalies, decreased intelligence, and neurological cretinism (which includes spasticity, deaf mutism, mental deficiency, and squint) [9]. Despite global public health efforts, iodine deficiency remains the leading preventable cause of mental retardation worldwide [12]. Severe iodine deficiency is also linked to intellectual development in early childhood in the absence of overt mental retardation. A 2005 meta-analysis of Chinese studies comparing intelligence quotient (IQ) of children living in naturally iodine-sufficient areas to children living in severely iodine deficient areas found that the IQ of iodine-sufficient children, on average, was 12.45 points higher [13].

2.2. Effects of Mild-to-Moderate Iodine Deficiency. The effects of mild-to-moderate iodine deficiency are less well understood than those of severe iodine deficiency. Hypotheses regarding the neurodevelopmental impact of mild-to-moderate maternal iodine deficiency are extrapolated from studies that examine the neonatal impact of mild maternal thyroid hypofunction on offspring. Pop et al. examined Bayley Scales of Infant Development scores among 10-month-old infants of women with fT4 levels below the tenth percentile in the first trimester of pregnancy compared to infants of women with higher fT4 levels at that gestational age [14]. The infants with lower maternal fT4 had significantly lower psychomotor scores. Henrich et al. studied expressive vocabulary at the age of 18 and 30 months in 3659 children of women with normal TSH but varying fT4 [15]. They found that lower maternal fT4 was associated with an increased risk of expressive language delay. Haddow et al. assessed the IQ of 7- to 9-year-old children of women with subclinical hypothyroidism in pregnancy, identified by elevated TSH in the second trimester, and found that IQ scores in these children averaged 7 points lower than children of matched women with normal thyroid function
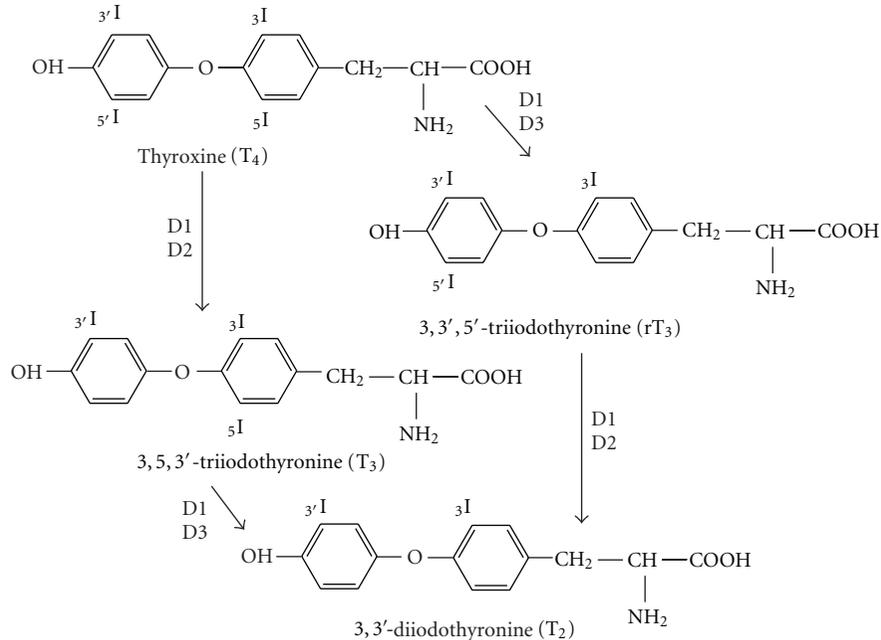
FIGURE 2: Thyroid hormone metabolism. D1: Type 1 deiodinase; D2: Type 2 deiodinase; D3: Type 3 deiodinase.

in the second trimester [16]. All of these studies underscore the impact of even mild thyroid hypofunction on fetal neurodevelopment. However, because they were conducted in iodine-sufficient areas, thus the thyroid hypofunction cannot be directly attributed to iodine deficiency.

A small study found a significantly greater prevalence of attention deficit hyperactivity disorder (ADHD) among the offspring of mothers from an area of mild-to-moderate iodine deficiency in comparison to those of mothers in a "marginally" iodine-sufficient area [17]. Vermiglio et al. followed these children over ten years, ultimately diagnosing 68.7% of the children from iodine-deficient areas with ADHD. In contrast, none of the children from the iodine-sufficient area were diagnosed with ADHD. 63.6% of the children diagnosed with ADHD were born to the mothers of the iodine-deficient area who were known to have been hypothyroxinemic early in gestation.

3. Assessment of Iodine Status

The World Health Organization (WHO)/International Council for the Control of Iodine Deficiency Disorders/United Nations Children's Fund (UNICEF) recommend median UIC as the primary tool for assessment of iodine status in pregnant populations [9]. This can be measured either over 24 hours or as a spot collection and can be expressed as mcg per liter or per gram creatinine. Because UIC is highly influenced by recent iodine intake, it can only be used to determine iodine status for populations, not for individuals [18]. Optimal median urinary iodine parameters are higher in pregnancy than the median values of 100–199 mcg/L consistent with iodine sufficiency in nonpregnant populations (Table 1).

TABLE 1: World Health Organization optimal median urinary iodine concentration values for populations [9].

Iodine sufficient population	Median UIC
Nonpregnant adult	100–199 mcg/L
Pregnant women	150–249 mcg/L
Lactating women	≥100 mcg/L

4. Iodine Nutrition in Pregnancy

4.1. Recommended Daily Intake. WHO recommends ingestion of approximately 250 mcg iodine daily for pregnant and lactating women [9]. The United States Institute of Medicine's recommended daily allowance for iodine is 220 mcg during pregnancy and 290 mcg during lactation [20]. The American Thyroid Association (ATA) strongly advocates adequate daily iodine intake in pregnancy, specifically recommending that women in North America take 150 mcg of iodine daily as a potassium iodide supplement during pregnancy and lactation in order to attain adequate levels [19] (Table 2).

4.2. Achieving Iodine Sufficiency. In many regions, the recommended iodine intake may be met by diet alone. Iodine enters the diet in multiple forms. In some regions, iodine is also present in drinking water. Worldwide, salt iodization is an ongoing effort springing from the recognition in the 20th century that inexpensive spraying of commercial salt with iodide can reverse iodine deficiency disorders [21]. In the USA women are exposed to iodine not only through iodized salt but also in other foods. Milk, yogurt, and other dairy products contain iodine as a result of the use of iodophor cleansers in the dairy industry and iodine supplementation

TABLE 2: World Health Organization (WHO) and Institute of Medicine (IOM) recommendations for dietary iodine intake [10, 19].

	WHO-recommended daily iodine intake	IOM-recommended daily iodine intake
Adequate intake for nonpregnant adult	150 mcg	150 mcg
Adequate intake in pregnant women	250 mcg	220 mcg
Adequate intake for lactating women	250 mcg	290 mcg

of cattle feed [22]. Some USA commercial breads contain high levels of iodine as well due to the use of iodate conditioners [23]. The most recent Total Diet Study by the U.S. Food and Drug Administration supports these two food groups as the main nonsalt sources for iodine in the U.S. [24]. In a market basket analysis, the average daily iodine intake among USA adults was calculated to be adequate at 138–353 mcg per person [24].

Despite ongoing availability of iodine in the diet and salt in the United States, National Health and Nutrition Examination Survey (NHANES) data demonstrates that the overall USA iodine intake has decreased over the past forty years from a median urinary iodine concentration of 320 mcg/L in 1970 to 160 mcg/L in 2003 [25]. The overall median UIC among pregnant women in the USA throughout from 2001 to 2006 was marginal at 153 mcg/L. NHANES 2005–2008 demonstrated that 35.3% of U.S. women of reproductive age had UIC < 100 mcg/L [25]. In the U.S., there is a higher prevalence of mild iodine deficiency in the pregnant population compared to the general population. The proportion of pregnant and reproductive aged nonpregnant women with UIC < 50 mcg/L has increased from 4% to 15% over the past 40 years, as documented by serial NHANES analyses [26]. These data suggest that in the U.S. an increasing proportion of this vulnerable population may be at risk for iodine deficiency. Worldwide, iodine deficiency remains an important public health problem, with an estimated 31% of the world's population still living in iodine-deficient regions [9].

4.3. Iodine Supplementation. If dietary iodine intake is insufficient, then supplementation is necessary. However, adequate supplementation is not currently easily achievable in the USA. A recent survey of all U.S. prescription and nonprescription prenatal vitamins revealed that only approximately 50% contained any iodine [27]. In prenatal multivitamins in which iodine was provided in the form of kelp, the amount of daily iodine was dramatically variable, making kelp an unreliable source for supplementation [27]. Among prenatal vitamins containing iodine in the form of potassium iodide, measured iodine levels were more reliable. However, when 150 mcg potassium iodide was listed as an ingredient, 23% of the mass was attributable to the potassium, thus providing only on average 119 mcg daily dose of iodide, lower than the 150 mcg daily dose recommended by the ATA. Worldwide, strategies to meet the iodine requirements set forth by WHO vary by region and local dietary intake [28].

4.4. Risks of Iodine Excess. There is controversy regarding the upper limit of acceptable iodine intake in pregnancy.

When iodine is present in great excess, the iodination of thyroglobulin is acutely inhibited via the acute Wolff-Chaikoff effect [29]. The mechanism is not well understood but is believed to involve newly formed iodolipids or iodolactones temporarily inhibiting thyroid peroxidase synthesis. After a few days, the thyroid is able to "escape" from the acute Wolff-Chaikoff effect, in part by downregulating NIS on the basolateral membrane and thereby modulating the influx of iodine entering into the thyroid [30]. The fetal thyroid gland does not acquire the capacity to escape from the acute Wolff-Chaikoff effect until approximately 36 weeks gestation [31]. Therefore, a maternal iodine load could potentially cause fetal, but not maternal, hypothyroidism. The Institute of Medicine recommends an upper limit of 1,100 mcg dietary iodine daily in pregnancy, while WHO recommends an upper limit of 500 mcg per day [9, 20]. The benefits of correcting iodine deficiency far outweigh the risks of supplementation as long as supplementation is not excessive [32]. Studies have demonstrated increased umbilical cord and fetal TSH in study groups given iodine supplementation. None, however, have demonstrated poor outcome among these neonates, and in contrast, two studies have demonstrated improved neurocognitive outcomes in these groups [33, 34].

5. Impact of Iodine Supplementation in Deficient Populations

5.1. Impact on Maternal Thyroid Function. Studies assessing the impact of iodine supplementation in mildly to moderately iodine-deficient women have had variable results with regard to maternal thyroid function. However, supplementation of iodine in this population appears overall safe. Romano et al. found increased thyroid size in 17 pregnant women receiving daily iodine supplementation in the form of 120–180 mcg iodized salt compared to 18 women who were not supplemented [35]. Pedersen et al. randomly assigned 47 iodine-deficient pregnant women to start either 200 mcg daily potassium iodide or placebo at 17–18 weeks of gestation [36]. The untreated group not only had increased thyroid volume but also increased maternal and cord blood thyroglobulin and maternal TSH. No difference was found in maternal or cord blood thyroid hormone levels. In contrast, Antonangeli et al. found no significant differences in maternal TSH, thyroid hormone, thyroglobulin, or thyroid volume in 67 pregnant women randomly assigned to 50 mcg or 200 mcg iodide daily as compared to controls [37]. Liesenkötter et al. similarly found no difference in maternal thyroid volume in 38 pregnant women supplemented with 300 mcg of iodine daily compared to controls and no difference in thyroid function

testing of mother or neonate [38]. Nohr and Laurberg found increased cord blood TSH in neonates from 49 mothers supplemented with a daily multivitamin that contained 150 mcg iodine compared with controls [39]. However, fT4 was slightly higher in the neonates of treated versus control mothers. While the results regarding impact on maternal and fetal thyroid function are variable, none of these early studies addressed neurocognitive outcomes in the offspring.

5.2. Iodine Supplementation in Severe Deficiency: Effects on Offspring. The first study to demonstrate that iodine supplementation in severe iodine deficiency significantly decreases the risk of cretinism was performed in the 1970s [40]. Severely iodine-deficient women in Papua New Guinea, regardless of pregnancy status, were given iodine supplementation. The offspring from the treated group had no evidence of cretinism, while 6% of infants born to untreated mothers had cretinism. Subsequent studies were conducted in Zaire, China, Peru, and Ecuador, areas known to be severely iodine deficient. All four studies demonstrated varying but consistently improved cognitive scores for children whose mothers received iodine supplementation during pregnancy [41–44].

5.3. Iodine Supplementation in Mild to Moderate Iodine Deficiency: Effects on Offspring. Recently, two studies have identified improved neurologic outcomes in the infants of mildly to moderately iodine-deficient women who received iodine supplementation early in gestation. Velasco et al. supplemented 133 pregnant women with 300 mcg of iodine daily during the first trimester of pregnancy and examined psychological development of the offspring at the age of 3–18 months compared to offspring of a group of 61 control women [33]. Upon initiation of supplementation, the treatment groups had adequate mean UICs of 153 mcg/L and 213 mcg/L among women initiated at less than and more than 10 weeks of gestation, respectively, both adequate according to WHO criteria. However, by the third trimester, significant differences were seen in the UICs of the treatment versus control groups. Treated women had a mean UIC of 203 mcg/L, while the control group's mean value was 87 mcg/L, consistent with mild-to-moderate iodine deficiency. Psychomotor assessment at 3–18 months was significantly higher in the offspring of the treated group. Within this group, psychomotor scores were also noted to be higher in offspring of women whose serum fT4 measurement remained stable throughout pregnancy in comparison to those whose fT4 declined.

Berbel et al. examined the effects of a 200 mcg daily iodine supplement in mildly to moderately iodine-deficient Spanish pregnant women [34]. Women were divided into three groups, one of which started iodine supplementation at 4–6 weeks of gestation, the second at 12–14 weeks, and the third only in the postpartum period. Consistent with prior studies, neurocognitive scores were significantly higher in groups who received iodine supplementation during pregnancy when compared to women who did not start until postpartum. Importantly, neurocognitive scores

were also significantly higher in the group who initiated iodine supplementation at 4–6 weeks of gestational age, during organogenesis, in comparison to those who began supplementation at 12–14 weeks of gestational age.

The effect of iodine supplementation on ADHD risk has not been studied.

6. Impact of Environmental Pollutants

Women with inadequate iodine nutrition in pregnancy may be particularly vulnerable to the effects of environmental thyroid disruptors. At pharmacologic doses, several environmental contaminants can affect iodine uptake at the thyroid and subsequent thyroid function. Exposures to low-dose perchlorate, thiocyanate, and nitrate are all ubiquitous in the United States. All three substances are competitive inhibitors of the sodium-iodine symporter (NIS) [45].

6.1. Perchlorate. Perchlorate is the most potent of the environmental NIS inhibitors, exhibiting roughly 30 times the affinity for NIS than iodine [46]. It is a byproduct of the manufacture of solid propellants used in rocket fuel. It has also been found in Chilean nitrate fertilizers used around the world. In the U.S., it is ingested in foods such as lettuce, wheat, and dairy and is detectable in low levels in groundwater in some regions [45]. Studies of perchlorate levels in infant formula found low levels in brands of U.S. formula tested [47, 48]. Perchlorate is remarkably stable not only in the environment but also in the human body, and thus exposure may be reliably assessed using urine concentrations. In vitro studies have demonstrated that at pharmacologic doses perchlorate decreases the active transport of iodine into tissue. There has been concern that low-level environmental exposure to NIS inhibitors could decrease iodine intake into the thyroid causing thyroid dysfunction and could also decrease NIS-mediated uptake of iodine into breast milk. The offspring of pregnant and lactating women would potentially be at highest risk for these effects [46].

The clinical impact of low-level environmental perchlorate on thyroid status in vulnerable populations remains unclear. An NHANES 2001-2002 analysis detected low levels of perchlorate in all urine samples ($n = 2820$) collected [49]. This large-scale study also demonstrated an inverse correlation between perchlorate and total T4 and a positive correlation with TSH in women but not men. This relationship was stronger among women with a UIC of < 100 mcg/L [50]. This effect on thyroid function has not been replicated in other studies. Several prospective studies administering increasing amounts of perchlorate to healthy human subjects have failed to demonstrate analogous changes in thyroid function other than a decrease in thyroidal iodine uptake at the highest doses [51–53]. Another cross-sectional study of environmental perchlorate exposure failed to find any association with first trimester thyroid function among 1600 iodine-deficient pregnant women [54]. While perchlorate has been identified in breast milk and colostrum in several small studies, there are no data yet to suggest that neonatal

consumption via breast feeding compromises the iodine status of the infant [47, 55].

6.2. Other NIS Inhibitors. Thiocyanate is a less potent competitive inhibitor of the NIS. It is a metabolite of cyanide produced from cigarette smoke and is found in various foods. Decreased T4, increased TSH, and thyroid enlargement have been reported among pregnant women who smoke [56]. Another study showed an association between cigarette smoking and decreased breast milk iodine concentration [57]. While compared to thiocyanate, perchlorate has 15 times the affinity for the NIS, the cumulative effects of one or both may still pose a risk to vulnerable populations.

Nitrate has a significantly lower affinity for NIS than either perchlorate or thiocyanate. However, it is omnipresent as a by-product of decomposition of organic materials. It is present in soil and groundwater and is found in virtually all crops, particularly root vegetables. Sodium nitrite is also used as a food preservative. The average daily adult intake of nitrate per day in the U.S. is 75–100 mg daily. Several recent studies from Bulgaria and Slovakia suggest an increased risk of goiter and subclinical hypothyroidism in iodine-sufficient areas with chronic exposure to very high nitrate concentrations. Small studies undertaken in the U.S. have failed to demonstrate the same association [45].

While the independent effect of these individual contaminants on iodine utilization and thyroid function may be small, it remains to be seen whether their cumulative exposure together with the national trend toward decreasing iodine intake among reproductive aged women in the U.S. may have adverse effects on thyroid function.

7. Conclusions

Women who are pregnant or lactating have increased dietary iodine requirements. Severe iodine deficiency leads to adverse maternal and fetal consequences. Even mild-to-moderate iodine deficiency in pregnancy has adverse effects on obstetric and neonatal outcomes. Recent data on the neonatal neurocognitive impact of early iodine supplementation suggests that adequate iodine intake should start as soon as the patient is aware she is pregnant, or, even better, should be incorporated as part of preconception planning. Research is needed on the impact of iodine supplementation in lactating women and their infants. Providers who care for pregnant women are encouraged to be aware of this essential micronutrient and counsel adequate iodine intake throughout preconception, pregnancy, and lactation.

Disclosure

All the authors have nothing to disclose.

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