Iodine metabolism

Iodine has fundamental role in thyroid hormone synthesis and is essential for the prevention of iodine deficiency disorders (IDD). Iodine content of the human body is 15–20 mg, of which approximately 70–80% is present in the thyroid gland. The essential requirement for normal growth is only 100–150 µg/day (1,2), because of which, iodine is referred to as a trace element. Iodine is a chemical element and unlike nutrients such as iron, calcium or the vitamins, does not occur naturally in specific foods. Iodine is found mainly in the ocean and after being converted into elemental iodine, is carried into the atmosphere, from where it returns to the land by rain and snow, however this return is so slow and small, and iodine deficiency in the soil continues. As a result, human and animal populations which are totally dependent on food grown in this soil become iodine deficient. In such areas use of iodized salt (via salt iodization) is the best way to provide daily iodine requirements (3,4).

Humans depend on exogenous sources of iodine to maintain the normal concentration of thyroid hormones (5,6). Iodine is rapidly absorbed through the gut, and following absorption is cleared from the circulation by the thyroid gland and kidney. In conditions of iodine sufficiency, thyroid gland takes up less than 10% of absorbed iodine, whereas in chronic iodine deficiency this fraction exceeds 80% (7,8). Physiologically, plasma iodine half-life is 10 hours, and in iodine deficiency or thyroid hyperfunction, this turnover is shortened (9). In lactating women, iodine is concentrates in the mammary gland where secretes it into breast milk to provide iodine for the newborn (10,11). When iodine intake is more than adequate, the excess iodine is readily excreted in urine. Approximately 90% of absorbed iodine is finally excreted by the kidney, therefore urinary iodine concentration (UIC) (expressed in µg/L) correlates well with the level of intake so it reflects the level

Review Article

Iodine nutrition in pregnancy

Hossein Delshad

Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence to: Hossein Delshad. Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Velenjac, Parvaneh Ave. No. 24 P. O. Box 19395-4763, Tehran, Iran. Email: delshad1336@yahoo.com.

Abstract: Due to its role as a component of thyroid hormones, iodine is considered an essential nutrient. These hormones cross the placenta early in pregnancy and are essential for brain development and maturation of the fetus during early pregnancy. The critical period for this dependency extends from intrauterine life to 3 years of age. Iodine requirements increase dramatically during pregnancy and lactation. Pregnant and breastfeeding women need extra iodine to help ensure their iodine needs are met. Inadequate iodine intake during these period leads to insufficient production of thyroid hormones. Severe iodine deficiency has negative effects on normal physical growth and mental development of children, whereas the consequences of mild to moderate deficiency are less clear. The elimination of iodine deficiency is relatively simple and feasible through iodine supplementation. Among the many methods of prevention, iodized oil and salt iodization programs have been implemented in many countries. Since 1999, the number of countries with effective salt iodization as a safe, cost-effective, and sustainable strategy to ensure sufficient intake of iodine has increased to the point that today over 80% of the world has access to adequately iodized salt. Although iodized salt is commonly the main source of iodine for general populations, iodine supplements are recommended by different medical societies during pregnancy and lactation.

Keywords: Iodine; pregnancy; lactation; iodized salt

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of recent iodine intake (12). Based on the recommendation of WHO, IGN (Iodine Global Network formerly ICCIDD) the median UIC in schoolchildren is the main indicator of iodine nutrition of a community. Urinary iodine excretion between 100 to 199 µg/L in school-aged children and adults, and between 150 to 249 µg/L in pregnant women are considered adequate (13). Iodine is necessary for thyroid hormone synthesis. It makes 65% and 59% of the weights of thyroxine (T4) and triiodothyronine (T3), respectively (2). The thyroid gland needs about 60 µg of iodine per day to produce adequate thyroid hormones. A very active iodine trapping mechanism which maintains a gradient of 100:1 between the thyroid cell and the extracellular fluid is responsible for this mechanism. In iodine deficiency state this gradient may exceed 400:1 for adequate synthesis of thyroid hormones by the thyroid gland (14).

**Impact of iodine deficiency**

Inadequate iodine intake has negative effects on physical and mental development of millions people living in iodine deficient areas worldwide and is hence considered an important nutritional deficiency and a major health problem (15). It mainly affects pregnant women, fetus and the neonate. In iodine deficiency thyroid hormone production decreases. Thyroid hormones regulate numerous physiologic processes, including growth, neurologic development, and reproductive function (8). Endemic goiter, enlargement of the thyroid gland, is the common manifestation of iodine deficiency (16). In chronic moderate to severe iodine deficiency, it is not possible for the enlarged thyroid to synthesize adequate thyroid hormones. Inadequate thyroid hormone production adversely affects growth and development and in particular damages the developing brain. The term IDD, introduced by Basil Hetzel in 1983 has transformed the world's understanding of the problem from endemic goiter to a wide range of conditions, indicating the vulnerability of the fetus and young children. IDD include mental retardation, other defects in development of the nervous system, goiter, growth retardation, reproductive failure, increased childhood mortality and is an economic burden (5) (Table 1).

<table>
<thead>
<tr>
<th>Life stage</th>
<th>Major disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal life and infancy</td>
<td>Abortion, stillbirth, congenital anomalies, increased infant mortality, psychomotor defects, cretinism in various degrees</td>
</tr>
<tr>
<td>Childhood and adolescence</td>
<td>Goiter, retarded physical development, impaired mental development, impaired intellectual performance</td>
</tr>
<tr>
<td>Adulthood</td>
<td>Goiter, hypothyroidism, impaired mental function</td>
</tr>
</tbody>
</table>

IDD, Iodine Deficiency Disorders.

Insufficient production of thyroid hormones damages the brain which, it severity depends on the time in life at which the deficiency occurs. During the first trimester of pregnancy, maternal thyroid hormones cross the placenta to serve as the primary source of this essential hormone to the fetus prior to the development of its own functional thyroid and may account for up to 20–40% of cord blood thyroid hormones at birth (17). The brain is particularly sensitive to iodine deficiency during its formation in early fetal and postnatal life. Its severity can vary from mild intellectual blunting to frank cretinism (18). Iodine deficiency also affects physical and psychomotor growth and development in early life, underscoring the importance for pregnant women.

Pregnancy alters normal thyroid gland function. Increased circulating estrogen during pregnancy increases thyroid binding globulin (TBG) by 2- to 3-fold and in response to this phenomenon and also because of thyrotropin stimulating hormone (TSH) receptor stimulation by human chorionic gonadotropin (hCH), thyroid hormone production increases by 50% during early gestation in pregnant women. Another change of thyroid hormone economy during pregnancy is degradation of thyroxin (T4) to bio inactive reverse triiodothyronine (rT3) by the placental type 3 inner ring deiodinase (19). On the other hand the glomerular filtration rate of iodide increases by 30% to 50% in early pregnancy. Altogether these physiological changes along with the need of fetal thyroid gland to iodine to produce thyroid hormones during the second half of gestation, increase iodine...
requirement in normal pregnancy (20, 21). In an iodine sufficient state, the maternal thyroid gland responses well to the changes of pregnancy. If these increased requirements of iodine are not met, it is not possible for either mother or fetus thyroid glands to produce adequate thyroid hormone, therefore they may develop thyroid enlargement (goiter) and thyroid insufficiency. Pregnancy loss, infant mortality, impairment of child development, irreversible brain damage and neurologic abnormalities are other complications of iodine deficiency during pregnancy (22). Iodine deficiency affects child development which can manifest itself as mild intellectual blunting to cretinism (23). The most serious form of IDD is endemic cretinism which is a permanent severely stunted physical and mental development due to severe maternal iodine deficiency (24). Even mildly iodine deficiency may be responsible for maternal hypothyroxinemia and hyperthyrotropinemia, which impair normal fetal and child neurodevelopment (25). It has been shown that 7- to 9-year-old children of untreated mildly hypothyroid mothers, on average, have 7 IQ points lower than the children of euthyroid control mothers (26). In the Dutch Generation R study, which included 3,659 mothers and their infants, severe maternal hypothyroxinemia was associated with expressive language and nonverbal cognitive delay in their infants at 30 months (27). There is debate regarding the effects of maternal subclinical hypothyroidism on the neuropsychological development of the fetus an association established by some studies in 1999 (28, 29). In addition observational studies over the last few decades have shown that subclinical hypothyroidism in pregnancy is associated with a lower-than-normal IQ in offspring (30-32). Subclinical hypothyroidism also increases the risks of preterm birth, placental abruption, admission to the neonatal intensive care unit and other adverse pregnancy outcomes including the neurodevelopmental retardation (33). However, it is not clear whether isolated hypothyroxinemia is also associated with these adverse outcomes in pregnancy (34, 35). Based on these results routine prenatal screening for and treatment of subclinical thyroid disease during pregnancy have been recommended by several professional organizations (36-38). Over 15% of pregnant women could be affected by this recommendation. However, the American College of Obstetricians and Gynecologists believes that it is still premature to recommend universal screening, because there are no trials showing beneficial effects of levothyroxine treatment on these outcomes (39). The Controlled Antenatal Thyroid Screening (CATS) study indicates that cognitive function in 3-year-old children was not better than that in controls, when mothers who had been found with subclinical thyroid failure or hypothyroxinemia were treated with levothyroxine (40). Despite this evidence, several scientific organizations recommend the treatment of subclinical hypothyroidism in their clinical practice guidelines (41, 42).

World status

Over the last century, considerable efforts world-wide have been made to control this nutritional problem, although many countries in the world are still iodine deficient. Globally, 29.8% of school-age children (246 million) have insufficient iodine intake and approximately two billion people worldwide are at risk of iodine deficiency (43, 44). During the past decade the number of iodine deficient countries has decreased from 54 to 20 while those with excessive iodine intake increased from 5 to 11. Worldwide currently 149 countries are iodine sufficient. It is estimated that 75% of households worldwide are consuming iodized salt. People who are living in the WHO regions of the Western Pacific and the Americas have the greatest access, which those in the Eastern Mediterranean region have the least access to iodized salt (45). Although studies of pregnant women and younger children are being conducted in many countries, data is limited as the majority of these countries still conduct routine iodine surveys in school-aged children. In 2016, the IGN reported that 69 countries had completed surveys in pregnant women. In 30 countries, the iodine intake of pregnant women was adequate and in 39 ones it was insufficient. It is reported that in some iodine sufficient countries like USA, Japan, Iran and etc. pregnant women are iodine deficient (46-49).

Iodine requirement

Adequate iodine nutrition is needed in all age groups for thyroid hormone production. Iodine requirements of women during pregnancy and lactation are increased to provide adequate iodine for her fetus and neonate. To meet the daily iodine requirements WHO, UNICEF, ING (13) and the American Institute of Medicine (50) have provided daily iodine intake recommendations for the different age groups (Table 2). The European Food Safety Authority recommendation is 200 µg iodine per day for pregnant and lactating women (53).

Excessive iodine intake can also be harmful, because it
inhibits thyroid hormone synthesis and its release into the circulation (Wolff-Chaikoff effect) (52). It is difficult to determine the threshold upper limit of iodine intake, because the amount of iodine intake before exposure to iodine excess has detrimental effect (51).

Table 3 shows the tolerable upper intake levels of iodine for different age groups.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>EC/SCF, 2002</th>
<th>IOM, 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>2–6</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>7–10</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>11–14</td>
<td>450</td>
<td>300</td>
</tr>
<tr>
<td>15–17</td>
<td>500</td>
<td>900</td>
</tr>
<tr>
<td>Adults</td>
<td>600</td>
<td>1,100</td>
</tr>
<tr>
<td>Pregnant women &gt;19 years</td>
<td>600</td>
<td>1,100</td>
</tr>
</tbody>
</table>


Iodine supplementation

Iodine is naturally present in some foods, is added to different foods, and is used as a dietary supplement. Seaweed, seafood, dairy products, grain products, and eggs are good sources of iodine, nevertheless most foods and beverage have low iodine and their iodine content is highly variable, they provide only 3 to 80 µg per serving (54). Accordingly most people need an additional source to provide adequate iodine for their daily requirements. Fortified salt, bread and water are the main sources of iodine. Iodized salt is table salt mixed with a minute amount of iodide and iodate, usually as the potassium salt. Salt iodization is the most common and cost-effective way of fortification (55). Salt was chosen as the medium because it is used by nearly all sections of a community. On the other hand its use is constant throughout the year. WHO recommends fortification of all food-grade salts with iodine as an effective and safe strategy for control and prevention of IDD in those living in both iodine deficient and iodine sufficient areas.

All scientific organizations believe that universal salt iodization (UIC) is the best public health measure to eliminate IDD. The benefits of iodine supplementation during pregnancy have been documented by many studies. In a randomized controlled trial in Papua New Guinea in 1970, pregnant women with severe iodine deficiency who were received injectable iodized oil (Lipiodol), were found to have decreased rates of fetal death, compared to untreated women (56). Decreased thyroid volume in mothers and infants and decreased maternal TSH levels also have been reported in women who received iodine during early pregnancy (57–61). Iodine supplementation during early pregnancy also has improved psychological and neurocognitive functions of infants (62,63). In one study no differences were observed between iodine-supplemented and un-supplemented pregnant women in respect of thyroid gland volume and maternal thyroid function parameters (64).

Recommendation for iodine intake

Most people receive relatively small amounts of iodine in their diet. Adults need 150 µg iodine per day, ranging from 90 to 290 µg per day, based on the individuals age and physiological status (65). As iodine is vital for healthy neurodevelopment in the fetus and in children, the iodine requirement increases during pregnancy and lactation to...
provide for the increased renal clearance of iodine and for the needs of the developing fetus and infant (66).

**Pre-pregnancy**

Women need many nutrients and trace minerals during preconception and in pregnancy. Iodine is one of the most important and essential micronutrients. Dietary modifications are necessary when a woman becomes pregnant, such as increasing the intake of iodine, which helps to ensure healthy fertility, conception and pregnancy. Restricted availability of iodine before pregnancy leads to thyroid problem before conception. Adequate intake of iodine in this period is associated with proper function of the thyroid gland and euthyroidism, which are essential for ovulation and fertility. Ideally intra-thyroidal iodine stores in women should be adequate by UIC programs, so the American Thyroid Association (ATA) has recommended 150 µg iodine daily as dietary supplements for all women 3 months before conception and during pregnancy and lactation both in iodine-deficient and iodine sufficient areas (49). This has been accepted by World Health Organization (WHO), UNICEF (13) and IGN (67).

**Pregnancy**

Based on the recent recommendations of both the Endocrine Society (41), and the ATA (43), all pregnant and lactating women should have daily intake at least 250 µg of iodine. Recommended daily iodine intakes by different agencies for pregnant women range between 220 to 250 µg and for lactating women between 250 to 290 µg (44-46,48,49).

**Conclusions**

Increased thyroid hormone requirement during pregnancy is the fundamental physiological adaptation, which begins in the first trimester of gestation. Adequate iodine nutrition during pregnancy and lactation is vital for thyroid hormone synthesis. Thyroid dysfunction and goitrogenesis are the most common and important outcomes of iodine deficiency during pregnancy. Therefore, all women during pregnancy and lactation need iodine prophylaxis. It has been shown that iodine prophylaxis and prevention of the iodine deficiency during pregnancy and lactation has decreased the rates of fetal death and endemic cretinism and prevented mental retardation in millions of young infants worldwide. Salt iodization is the effective and safe method to provide iodine requirements of the community, although it is not the ideal source, especially during pregnancy and breastfeeding. According to recent guidelines of scientific organizations all pregnant and breastfeeding women should take a multivitamin containing 150 µg of iodine, not only in iodine deficient regions, but also in iodine sufficient areas.

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**Footnote**

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