Iodine Deficiency from Pregnancy to Childhood

13

Caterina Di Cosmo, Massimo Tonacchera, and Paolo Vitti

13.1 Introduction

13.1.1 Iodine Sources and Metabolism

Iodine is a micronutrient essential for mammalian life because it is critical for the synthesis of thyroid hormones, thyroxine (T_4), and triiodothyronine (T_3), which contain in their molecules four and three atoms of iodine, respectively. Thyroid hormones (TH) are important for the growth and development of different tissues, especially the central nervous system and the skeleton, for the cardiac and gastrointestinal function, and for the regulation of the energy homeostasis throughout life. Disturbances in TH availability during early embryonic development, as in maternal iodine deficiency, cause severe neurological abnormalities in the newborns [1]. The World Health Organization (WHO) considers iodine deficiency to be "the single most important preventable cause of brain damage" worldwide [2]. Despite the great improvements in global iodine nutrition in the last century, it is currently estimated that iodine deficiency still affects 241 million school-aged children [3].

The only source of iodine is the diet. While most iodine is found in the oceans, its amount in potable water and vegetables and then in animal food is poor in many areas, where it was removed by the surface soil because of wide glaciations. Only foods of marine origin have high iodine content because marine plants and animals

C. Di Cosmo • M. Tonacchera
Department of Clinical and Experimental Medicine, Endocrinology Unit, University Hospital, University of Pisa, Pisa, Italy

P. Vitti (✉)
Department of Clinical and Experimental Medicine, Endocrinology Unit, University Hospital, University of Pisa, Via Paradisa 2, Pisa 56124, Italy
e-mail: paolo.vitti@med.unipi.it

G. Bona et al. (eds.), *Thyroid Diseases in Childhood: Recent Advances from Basic Science to Clinical Practice*, DOI 10.1007/978-3-319-19213-0_13

are able to concentrate iodine from seawater. Therefore, in the absence of iodine prophylaxis programs, iodine intake may be insufficient. More commonly affected by iodine deficiency are the extraurban populations, especially rural, that eat non-industrial local foods, poor in iodine. Indeed, the economic status more than the geographic location is the main determinant of the quality of the food and of its iodine content. In many countries, salt, bread, and milk are fortified with iodine, as an effort to eradicate iodine deficiency. Other sources of iodine are compounds used by industry and agriculture as well as supplements and disinfectants and medicines.

The iodine contained in the food is absorbed by about 90 % in the stomach and duodenum [4]. The absorbed iodine and that resulting from the peripheral metabolism of thyroid hormones and iodothyronines constitute the extrathyroidal pool of inorganic iodine, which is in equilibrium with the thyroid and the kidneys. The human body contains a small amount of iodine, 70–80 % of which is concentrated by the thyroid [5] through the sodium iodide symporter (NIS) that is located on the basolateral surface of thyrocytes [6]. On the apical surface of the thyrocytes, the thyroperoxidase (TPO) catalyzes the synthesis of monoiodotyrosine (MIT) and diiodotyrosine (DIT) and then the coupling of two DITs to produce T_4 or of a MIT and a DIT to produce T_3. A normal adult utilizes about 80 μg/day of iodine to produce thyroid hormones, 55 μg of which come from the diet and 25 μg from the peripheral metabolism of TH. Ninety percent of the plasma iodine is excreted by the kidney and only a small amount in the feces. When iodine intake is slightly insufficient (i.e., <100 mg/day), TSH induces a higher NIS expression with an increase of thyroid iodine uptake and preferential synthesis of T_3, thus allowing a normal content of intrathyroidal iodine. In chronic iodine deficiency, the thyroid content of iodine progressively decreases, the metabolic balance of iodine becomes negative, and goiter and hypothyroidism with its sequelae ensue.

The thyroid content in iodine of fetal thyroid changes with the gestational age: it is very low during the first stages of development, increases quickly after the 15th week of gestation, when the thyroid starts to actively concentrate the iodine, and reaches a plateau at the end of gestation. The total content in iodine of the thyroid of full-term newborns depends on the dietary iodine intake. Compared to adults, newborns and infants have less effective adaptative mechanisms to iodine deficiency.

13.1.2 Modification of Thyroid Function and Iodine Metabolism During Pregnancy

An adequate iodine intake is particularly important during pregnancy for the possible consequences of iodine deficiency (ID) both on the mother and fetus. Pregnancy is associated with relevant changes in thyroid physiology [7] (Fig. 13.1). During early gestation, serum thyroxine-binding globulin (TBG) increases markedly, under the influence of elevated estrogen concentration, and the clearance of plasma iodine increases as a consequence of the higher glomerular filtration. ID induces a relative hypothyroxinemia (low T4 levels) in pregnancy, which in turn stimulates TSH secretion, enhances thyroid

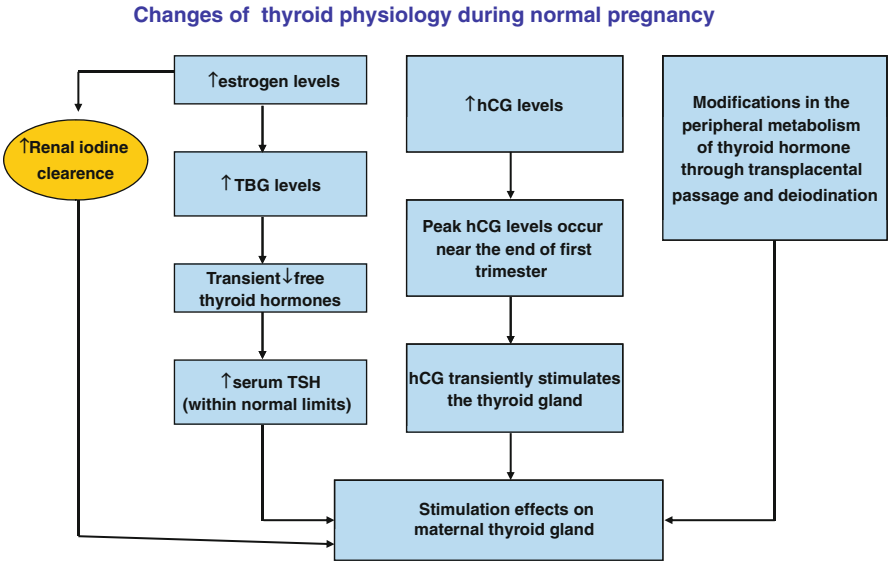

Fig. 13.1 The scheme shows the mechanisms which concur in the stimulation of maternal thyroid function during a normal pregnancy (Modified from Ref. [7])

stimulation, and increases thyroid volume in both the mother and the fetus. At the end of the first trimester, there is a transient thyroid stimulation by high levels of human chorionic gonadotropin (hCG) while during the second half of the gestation the placental type 3 iodothyronine deiodinase increases the metabolism of maternal T_4. As a consequence, the maternal thyroid gland is required to increase its hormonal production, through an increase of iodine uptake and a depletion of intrathyroidal stores. Later in gestation, the passage of iodine to the fetal-placental unit is another cause of deprivation of maternal iodine. For these reasons, as described in European areas with mild iodine deficiency, there is an increase of goiter formation during pregnancy that is only partially reversible postpartum. In addition, iodine deficiency correlates with a larger thyroid volume in newborns, and therefore goiter formation may start during the fetal thyroid development [7]. In presence of severe maternal iodine deficiency during pregnancy, there is a reduction in maternal thyroxine production, inadequate placental transfer of maternal thyroxine, and impairment of fetal neurological development.

13.1.3 Iodine Requirements

Although with some limitations, several studies have established the iodine requirement at different age and physiological conditions.

The WHO recommends 90 μg of iodine daily for infants and children up to 5 years, 120 μg for children 6–12 years, 150 μg daily for children ≥12 years and

Table 13.1 WHO recommendations for iodine intake by age or population group (Ref. [2])

Age or population group	Iodine intake (μg/die)
Children 0–5 years	90
Children 6–12 years	120
Children ≥12 years/ adults	150
Pregnancy	250
Lactation	250

adults, and 250 μg daily during pregnancy and lactation [2] (Table 13.1). The US Institute of Medicine–recommended minimum daily intake of iodine is similar: 90 μg daily for children 1–8 years old, 120 μg for children 9–13 years, 150 μg daily for older adolescents and nonpregnant adults, 220 μg for pregnant women, and 290 μg for lactating women [8].

The iodine requirements are higher in pregnant women because of the above-listed changes in thyroid physiology.

13.1.4 Assessment of Iodine Intake

The methods for the assessment of iodine nutrition in the populations are goiter prevalence, urinary iodine concentration (UIC), serum TSH in newborns, and serum thyroglobulin (Tg). The urinary iodine concentration indicates current iodine nutrition, while thyroid size and the serum thyroglobulin concentration reflect iodine nutrition over a period of months or years.

Goiter goiter can be measured by neck inspection and palpation or by thyroid ultrasonography. According to WHO/ICCIDD, grade 0 is a thyroid that is not palpable or visible, grade 1 is a goiter that is palpable but not visible when the neck is in the normal position, and grade 2 is a goiter that is clearly visible when the neck is in a normal position. Thyroid ultrasound is more sensitive and specific than palpation but requires valid references of thyroid volume data. Goiter surveys as indicators of iodine sufficiency are usually done in school-age children because they are easily recruitable and hopefully reflect the actual impact on humans of iodine deficiency, although enlarged thyroids in children who were iodine deficient during the first years of life may not regress completely after introduction of salt iodization [9]. The WHO has established total goiter rate in schoolchildren to define severity of iodine deficiency in populations: below 5.0 % indicates iodine sufficiency, 5.0–19.9 % mild deficiency, 20.0–29.9 % moderate deficiency, and above 30.0 % severe deficiency. In addition, a reduction of goiter rate by ultrasound indicates that iodine deficiency has disappeared, and therefore a frequency of goiter under 5 % in schoolchildren must be considered as a parameter of iodine sufficiency [10].

Urinary iodine concentration because >90 % of dietary iodine eventually appears in the urine, the UIC is an excellent indicator of recent iodine intake. It is measured in spot urine specimens from a representative sample of a population and expressed as the median, in μg/L. The median urinary iodine concentration in a population has been

Table 13.2 Epidemiological criteria from WHO for assessment of iodine nutrition in school-aged children, pregnant and lactating women, and infants based on median or range of UI (Ref. [2])

UI (μg/L)	Iodine intake	Iodine nutrition
School-aged children		
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimum
>200	More than adequate	Risk of iodine induced hyperthyroidism
>300	Excessive	Risk of adverse health consequences
Pregnant women		
<150	Insufficient	
150–249	Adequate	
250–499	More than adequate	
≥500	Excessive	
Lactating women		
<100	Insufficient	
≥100	Adequate	
Children less than 2 years		
<100	Insufficient	
≥100	Adequate	

used to develop a system for classifying iodine deficiency and sufficiency (Table 13.2) [2]. The most usual survey group is school-age children, but their nutrition must reflect that of the community in order for the data to be meaningful. Mild iodine deficiency is defined as a median urinary iodine concentration of 50–99 μg/L, moderate deficiency as 20–49 μg/L, and severe deficiency as <20 μg/L [11]. Pregnant women require special attention because their renal threshold for iodine is lower, the needs of the fetus are greater, and dietary salt (including iodized salt) is often restricted [12, 13]. In pregnant women, urinary iodine concentrations of 150–249 μg/L are considered adequate [14].

TSH TSH concentration obtained during the neonatal screening of congenital hypothyroidism (CH) is useful to assess iodine nutrition, because the increase of fetal TSH is an adaptative mechanism to iodine deficiency. Compared with the adult, the newborn thyroid contains less iodine but has higher rates of iodine turnover. When iodine supply is low, maintaining high iodine turnover requires increased TSH stimulation. Therefore, iodine deficiency causes a shift toward higher TSH values in the neonatal screening of CH. A TSH value >5 mU/L in whole blood collected 3–4 days after birth that lasts for few weeks in more than 3 % of newborns indicates iodine deficiency in the population [2]. Studies suggest also that newborn TSH is a sensitive indicator of iodine nutrition during pregnancy along with determination of the median UIC [15].

Serum Tg Tg is the most abundant intrathyroidal protein. Serum Tg is higher in iodine-deficient than in iodine-sufficient areas as a consequence of the TSH

stimulation and the higher rate of goiter, and its concentrations fall quickly with the implementation of iodine prophylaxis. In iodine-deficient infants and children, serum Tg concentrations are high more often than are serum TSH concentrations. Although a nonspecific test, since any type of thyroid stimulation or injury can raise the serum Tg concentrations, the values correlate well with the severity of iodine deficiency. Tg has also been shown to be a sensitive measure of excess iodine intake in school-age children [16]. Moreover, in one study the serum Tg level was better than thyroid volume measurement by ultrasound as an indicator of iodine nutrition [17].

13.2 Consequences of Iodine Deficiency

The clinical consequences of inadequate iodine intake are collectively termed "the iodine deficiency disorders" (IDD) (Table 13.3) [18]. When severe iodine deficiency occurs during pregnancy, it is associated with cretinism and increased neonatal and infant mortality. Mild iodine deficiency is associated with thyroid enlargement and learning disabilities in children. All these consequences of iodine deficiency stem from the associated hypothyroidism.

Additional factors that can exacerbate the effects of iodine deficiency include coexistent deficiencies of iron, selenium, and vitamin A [19] and the ingestion of foods such as cassava or millet containing goitrogenic substances.

Goiter is the most frequent manifestation of iodine deficiency and can affect individuals of all ages. It represents a compensatory response to iodine deficiency. Low iodine intake leads to reduced T_4 and T_3 production, which results in increased TSH secretion in an attempt to restore iodothyronine production to normal. TSH also stimulates thyroid growth. The goiter is initially diffuse but eventually becomes nodular because the cells in some thyroid follicles proliferate more than others.

Table 13.3 Iodine deficiency disorders (IDD) by age group

Age groups	Consequences of iodine deficiency
All ages	Goiter
Fetus-neonate	Abortion
	Stillbirth
	Congenital anomalies
	Perinatal and infant mortality
	Endemic cretinism
	Overt or subclinical hypothyroidism
Infant-child/ adolescent	Impaired mental function
	Delayed physical development
Adult	Toxic nodular goiter
	Iodine induced hyperthyroidism
	Hypothyroidism
	Endemic mental retardation
	Decreased fertility rate

Therefore, in regions of iodine deficiency, children and adolescents generally have diffuse goiters, while adults who lived in conditions of long-standing iodine deficiency have nodular goiter.

This chapter will focus on the consequences of iodine deficiency from fetal life to childhood.

13.2.1 Consequences of Iodine Deficiency During Pregnancy and Infancy

13.2.1.1 Neurological Development

Goiter is the most common clinical manifestation of iodine deficiency, but another important consequence is a defective development of central nervous system because brain development depends on thyroid hormones during fetal and early postnatal life.

THs have no influence on very early stages of neurological development but regulate its later processes, which include neurogenesis, myelination, dentrite proliferation, and synapse formation [20, 21]. In particular, three stages of thyroid hormone–dependent neurological development can be recognized. The first occurs before the onset of fetal thyroid hormone synthesis, which occurs at 16–20 weeks post conception in humans. During this period, TH exposure comes only from maternal hormones [1, 22] and influences proliferation and migration of neurones in the cerebral cortex, hippocampus, and medial ganglionic eminence [23, 24]. The second stage occurs during the remainder of pregnancy after the onset of fetal thyroid function when the developing brain derives its supply of TH from both the fetus and the mother [1, 22]. During this period, thyroid hormone regulates neurogenesis, neuron migration, axonal outgrowth, dendritic branching, and synaptogenesis, together with the initiation of glial cell differentiation and migration and the onset of myelination [25]. The third stage occurs in the neonatal and postnatal period when thyroid hormone supplies to the brain entirely derive from the child and are critical for continuing maturation. During this period, while continuing gliogenesis and myelination, THs regulate migration of granule cells in the hippocampus and cerebellum, pyramidal cells in the cortex, and Purkinje cells in the cerebellum [25].

The frequency and severity of the neurological impairment are proportional to the magnitude of iodine deficiency. In areas of severe chronic iodine deficiency, maternal and fetal hypothyroxinemia can occur from early gestation onward.

13.2.1.2 Endemic Cretinism

The clinical manifestations caused by chronic severe iodine deficiency are referred to as endemic cretinism. In its classical description, endemic cretinism includes a neurological and a myxedematous form [26].

The neurological cretinism presents with severe mental retardation with squint, deaf-mutism, motor spasticity, and goiter. The mental deficiency is characterized by a marked impairment of abstract thought, whereas autonomic and vegetative functions and memory are relatively well preserved, except in the most severe cases. The

motor disorder is characterized by proximal rigidity of both lower and upper extremities and the trunk, whereas spastic involvement of the feet and hands is unusual, therefore most cretins can walk.

The myxedematous form has less severe mental retardation and more pronounced hypothyroid features, including severe growth retardation, incomplete maturation of the facial skeleton with naso-orbital configuration abnormalities and atrophy of mandibles, puffy features, dry and thickened skin, dry and rare hair, and delayed sexual maturation. In this form, goiter is usually absent, and the thyroid is usually atrophic.

In many instances, cretinism may present as a mixed form with features of both. Therefore, it can be often difficult to differentiate the two forms [27].

Studies suggest that selenium deficiency combined with severe iodine deficiency can more specifically induce forms of atrophic rather than goitrous hypothyroidism and therefore of myxedematous rather than neurological cretinism [28]. Selenium is normally present in high concentrations in the normal thyroid and is essential for the synthesis of selenoproteins such as glutathione peroxidase (GPX), which acts as antioxidant, and type I 5'-deiodinase, which metabolizes thyroid hormones. The mechanism would be the following: iodine deficiency causes thyroid hyperstimulation by TSH that leads to increased production of H_2O_2 within the thyroid follicular cells; selenium deficiency also results in accumulation of H_2O_2 due to GPX deficit. Excess of H_2O_2 can induce thyroid cell destruction and myxedematous cretinism. On the other hand, deficiency of the selenoenzyme 5′-deiodinase causes decreased catabolism of T_4–T_3 with increased availability of T_4 for the fetal brain and prevention of neurological deficits; T_4, in fact, crosses the brain–blood barrier more easily than T_3.

Cases of overt myxedematous, neurological, or mixed endemic cretinism are reported in areas of severe iodine deficiency such as Africa and Asia.

The only way to prevent neurological cretinism is by administration of iodine to women early in gestation or even before they become pregnant. In a randomized trial and several population-based studies of women living in severely iodine-deficient regions, iodine supplementation to women prior to conception or during early pregnancy was associated with substantially better neurological and developmental outcomes in children [29–31].

13.2.1.3 Subclinical Neurological Defects

Severe iodine deficiency has been almost eradicated through extensive iodine prophylaxis programs worldwide. As a consequence, new cases of cretinism have disappeared. However, several regions of mild to moderate iodine deficiency still exist [32].

Several reports have described cases of neurological deficits or minor neuropsychological impairments also in children born to mothers exposed to mild to moderate iodine deficiency during pregnancy. These defects may be detected by appropriate neuropsychological tests [33]. In Tuscany, neuropsychological performance was tested in 107 children living in a village characterized by mild iodine deficiency (UIC = 64 μg/L) by a block design subtest of the Wechsler Intelligence Scale for

Children and simple reaction times to visual stimuli. The results obtained in these children were compared with those obtained in children born and living in an iodine-sufficient area. The block design test was not different between the two groups of children, while reaction times were significantly delayed in children living in the iodine-deficient village. These data indicate that mild iodine deficiency may impair the rate of motor response to perceptive stimuli even in the absence of general cognitive defects. Mild to moderate iodine deficiency was also shown to be associated with minor neurological deficits in Sicily [34].

However, randomized trials of iodine supplementation to pregnant women with mild to moderate iodine deficiency have reported mixed results in terms of improvements of thyroid function parameters, which may be considered as surrogate markers of future infant development [35]. In some but not in all trials [36, 37], iodine supplementation resulted in smaller thyroid volumes and lower Tg concentrations in mothers and/or newborns compared with controls. Indeed, there was no effect on maternal or neonatal T_4 concentrations in the majority of the trials. Moreover, no final conclusion can be drawn from these studies because child cognitive outcomes were not measured.

An increased auditory threshold may be another clinical manifestation of iodine deficiency. As an example, in a study of 150 school-age children in Spain, 38 % had a goiter [38]. In this subset, there was an inverse relationship between auditory threshold and urinary iodine excretion (i.e., the more iodine deficient, the higher the auditory threshold).

The potential adverse effects of mild to moderate iodine deficiency during pregnancy on cognitive and/or neurological function of the offsprings are still uncertain.

Two prospective case–control studies have reported even mild thyroid dysfunction during pregnancy may impair cognitive development of the offspring [39, 40]. Children exposed to maternal hypothyroxinemia presented reduced IQ scores, subtle deficits in cognition, memory, visuospatial ability [39], and delayed mental and motor function [40]. Animal models confirmed that maternal hypothyroxinemia induced in a critical period of active neurogenesis resulted in alteration in cell migration and cytoarchitecture of the cortex and hyppocampus in the 40-day-old progeny [23, 41]. The limitation of these previous studies is that they were conducted in iodine-sufficient areas.

In two following observational studies of women with mild to moderate iodine deficiency and mild hypothyroxinemia, neurodevelopmental outcomes were better in children whose mothers received iodine supplementation (200–300 μg potassium iodide daily) early in pregnancy (prior to the 10th week of gestation) compared with children whose mothers did not [42, 43]. The better outcomes noted in these studies may be related to improvement in maternal hypothyroxinemia. Both mild and severe maternal hypothyroxinemia have reportedly been associated with a higher risk of expressive language delay in newborns [44]. Severe maternal hypothyroxinemia also predicted a higher risk of nonverbal cognitive delay. It is possible that iodine supplementation in women with iodine deficiency severe enough to cause maternal hypothyroxinemia may improve neurodevelopmental outcomes, but this has not been assessed in randomized trials.

13.2.1.4 Birth Weight and Infant Growth

There is evidence that correction of iodine deficiency during pregnancy in severely iodine-deficient areas determines improvements of head circumference and birth weight of offspring.

In an area of western China, iodine repletion of pregnant women reduced the prevalence of microcephaly from 27 to 11 % [29]. In studies conducted in Algeria and Zaire, treatment of women with oral iodized oil just before conception or early in pregnancy resulted in respectively 6.25 % and 3.7 % higher birth weight compared with offspring of untreated mothers [45, 46]. (For the relationship between iodine deficiency and somatic growth, see Sect. 13.2.2.2.)

13.2.1.5 Neonatal and Infant Mortality

Severe iodine deficiency increases neonatal and infant mortality, an effect that can be reduced by up to 50 % with correction of severe iodine deficiency [47]. The mechanism of this benefit is not known, but multiple factors are probably involved. Hypothyroid or retarded infants may suffer more birth trauma and be more prone to infectious diseases and nutritional deficiencies typical of the poor rural communities in which iodine deficiency is so prominent.

13.2.2 Consequences of Iodine Deficiency in Childhood

13.2.2.1 Intellectual Disability

Iodine deficiency appears also to have adverse effects on growth and development in the postnatal period. Children and adolescents in regions of iodine deficiency are at risk for some degree of intellectual disability and fine motor skill abnormalities compared to children in iodine-sufficient areas.

A meta-analysis of 21 observational and experimental studies relating iodine deficiency to cognitive development suggested that iodine deficiency alone caused an average loss of 13.5 IQ points in affected subjects [48]. This evidence is suggestive, although the developmental studies in iodine-deficient regions have many limitations; among these are the inability to distinguish between the persistent effects of fetal iodine deficiency and the ongoing effects of iodine deficiency in childhood and adolescence and the presence of other environmental factors which may affect child development (i.e., socioeconomic status, accessibility and quality of education and health).

Even in developed countries, marginal iodine sufficiency may lead to intellectual compromise [49]. In Jaen province, in Spain, schoolchildren with UI below 100 μg/L had lower IQ scores: 96.4 versus 99.0 in schoolchildren with UI greater than 100 μg/L [50]. In Australia, children born to mothers with urinary iodine concentrations during pregnancy of less than 150 μg/L compared with ≥150 μg/L had reductions in spelling, grammar, and English-literacy standardized test scores at age 9 years [51]. The children grew up in a region considered to be iodine replete (median UI 108 μg/L), and therefore, the results reflect the effects of fetal rather than childhood iodine insufficiency.

Intellectual disability resulting from the effects of iodine deficiency on the central nervous system during fetal development is not reversible. In contrast, the additional impairment caused by continuing postnatal hypothyroidism and/or iodine deficiency may improve with appropriate thyroid hormone replacement and/or iodine supplementation [52]. In a double-blind intervention trial of iodine supplementation or placebo in 310 10- to 12-year-old children in Albania, iodine supplementation with 400 mg of iodine as oral iodized oil significantly improved thyroid function (prevalence of hypothyroxinemia was reduced from approximately 30 to <1 %) and performance on cognitive testing evaluating information processing, fine motor skills, and visual problem solving [53].

13.2.2.2 Somatic Growth

It is known that severe iodine deficiency in womb causes cretinism and dwarfism, while iodized oil given during pregnancy in areas of moderate iodine deficiency increases birth weight by 100–200 g [45]. More controversial is the relationship between iodine deficiency and postnatal growth. However, most of the cross-sectional studies on iodine intake and child growth showed modest positive correlation [35].

Iodine status may influence growth through its effects on thyroid function. Thyroid hormone promotes growth hormone (GH) secretion and modulates the effects of GH at receptor level [54, 55]. Insulin-like growth factor (IGF)-1 and IGF-binding protein (IGFBP)-3 are also dependent on thyroid status. Indeed, hypothyroidism decreases circulating IGF-I and IGFBP-3 levels, whereas thyroid hormone replacement increases them [56, 57]. A controlled study including 10- to 14-year-old children from Morocco, Albania, and South Africa who were given iodine as iodized salt or oil and placebo showed that the increase in median UI to >100 μg/L was associated to an increase in IGF-1 and IGFBP-3 concentrations and an improvement in somatic growth [58].

13.2.2.3 Subclinical Hypothyroidism

Compared with the adult, the child thyroid contains less iodine but has higher rates of iodine turnover. Therefore, chronic iodine deficiency causes in children more than in adults an increase in TSH concentrations and a thyroid hormone pattern consistent with subclinical hypothyroidism (SH). Because SH is associated with cardiovascular disease risk factors [59], such as abnormalities in the lipid profile, correction of iodine deficiency may be beneficial also in reducing these risks. This effect of iodine supplementation has been reported in a recent controlled study, in which treatment of moderately iodine-deficient children affected by SH due to iodine deficiency improved their lipide profile and reduced insulin levels compared with controls [60]. However, more studies are needed to confirm the findings.

13.3 Prophylaxis and Treatment of Iodine Deficiency

An optimal correction of iodine deficiency should be carried out at the level of the community rather than the individual.

13.3.1 Salt Fortification with Iodine and Other Options

Iodization of salt is the preferred method of increasing iodine intake in a community, because salt is consumed by everyone, it is technically easy to produce, does not change salt taste, and the cost is relatively low.

However, the iodization of all salt for human and livestock consumption (Universal Salt Iodization – USI) is not commonly achieved. The usual dose for salt fortification is between 20 and 40 mg of iodine/kg of salt (sodium chloride) as potassium iodide or iodate. The optimal amount to be added for a particular country or region can be calculated from the daily per capita salt consumption, the amount of iodine consumed from other sources, and any losses of iodine between production and consumption.

Alternatives are needed when salt iodization is impractical or delayed. In these cases, effective options are iodized oil (Lipiodol), iodized water, and iodine tablets or drops. Lipiodol, developed as a radiographic contrast agent, contains 480 mg iodine/mL. A single oral dose of 0.5–1.0 mL provides an adequate amount of iodine for 6 months to 1 year; intramuscular administration of the same dose provides an adequate amount for 2–3 years [61]. Iodized oil is more expensive than salt iodization and requires direct administration to each subject. If given intramuscularly, it requires skilled administration and has a risk of infection if improper technique is used. Its main advantage is that it can be implemented promptly. It has been especially valuable for women of childbearing age and children in regions of severe iodine deficiency.

Water is another occasional iodization vehicle because it is a daily necessity like salt.

Other methods of iodide administration include oral administration of potassium iodide solution every 2–4 weeks and daily administration of tablets containing from 100 to 300 μg potassium iodide. The latter is particularly recommended to meet the increased needs for iodine during pregnancy and lactation, and it can be routinely incorporated into prenatal vitamin/mineral preparations. In addition, alternative methods of food iodine enrichment are currently under study. Hydroponic experiments were carried out to investigate the possibility of enriching the iodine uptake by spinach [62] or other vegetables such as tomatoes and potatoes. A recent study [63] tested the efficiency of vegetables (potatoes, cherry tomatoes, carrots, and green salad) fortified with iodine in a group of 50 adult healthy volunteers. A daily intake of 100 g of vegetables containing 45 μg of iodine (30 % of the Recommended Daily Allowance), increased after 2 weeks the UIC by about 20 %, showing that the biofortification of vegetables with iodine can determine a mild but significative increase in UI concentration and, along with the habitual use of iodized salt, may contribute to improve the iodine nutritional status of the population without risks of iodine excess.

13.3.2 Iodine Needs During Pregnancy and Lactation

In regions where <90 % of households use iodized salt and the median UIC in children is <100 μg/L, the WHO recommends iodine supplementation in pregnancy and

lactation (250 μg daily) [14]. In pregnant women, urinary iodine concentrations of 150–249 μg/L indicate adequate iodine intake.

In the USA, women who do not consume dairy products or iodized salt may have lower urinary iodine concentrations [64]. The American Thyroid Association recommends that women from the USA receive a supplement of 150 μg of iodine (in the form of potassium iodide) daily during pregnancy and lactation, which is the dose included in the majority of prenatal vitamins marketed in the USA [13]. The Institute of Medicine recommended minimum daily intake is somewhat higher: 220 μg for pregnant women and 290 μg for lactating women .

13.3.3 Adverse Effects

Iodine repletion in the doses used for iodization of salt and in prenatal supplements has few adverse effects. Iodine administration may result in hyperthyroidism in patients with endemic goiter or in patients with nodular goiters containing autonomously functioning tissue. In contrast, iodine administration may induce or exacerbate hypothyroidism in patients with underlying autoimmune thyroiditis. In regions of iodine deficiency, both hyperthyroidism and hypothyroidism have been reported after the introduction of iodine [65, 66].

Excessive iodine ingestion during pregnancy may have adverse effects on fetal thyroid function. Indeed, a sudden exposure to excess serum iodine inhibits organification of iodine through the Wolff-Chaikoff effect [67]. The fetal thyroid gland, which has not full functioning mechanisms of escape from the Wolff-Chaikoff effect, is particularly susceptible to the inhibitory effects of excess iodine, and this can result in a prolonged inhibition of thyroid hormone synthesis, an increase in TSH, and fetal goiter.

The tolerable upper intake amount for iodine, as established by European and US expert committees, ranges from 600 to 1100 μg daily for pregnant women >19 years of age [68]. For adolescents 15–17 years, it ranges from 500 to 900 μg daily and for younger children 200–450 μg/day.

References

1. de Escobar GM, Obregon MJ, del Rey FE (2004) Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pract Res Clin Endocrinol Metab 18:225–248
2. WHO UI (2007) Assessment of iodine deficiency disorders and monitoring their elimination, 3rd edn. World Health Organization, Geneva
3. Andersson M, Karumbunathan V, Zimmermann MB (2012) Global iodine status in 2011 and trends over the past decade. J Nutr 142:744–750
4. Alexander WD, Harden RM, Harrison MT, Shimmins J (1967) Some aspects of the absorption and concentration of iodide by the alimentary tract in man. Proc Nutr Soc 26:62–66
5. Fisher DA, Oddie TH (1969) Thyroid iodine content and turnover in euthyroid subjects: validity of estimation of thyroid iodine accumulation from short-term clearance studies. J Clin Endocrinol Metab 29:721–727

6. De La Vieja A, Dohan O, Levy O, Carrasco N (2000) Molecular analysis of the sodium/iodide symporter: impact on thyroid and extrathyroid pathophysiology. Physiol Rev 80:1083–1105
7. Glinoer D (2004) The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. Best Pract Res Clin Endocrinol Metab 18:133–152
8. Institute of Medicine AoS (2001) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. National Academy Press, Washington, DC
9. Aghini-Lombardi F, Antonangeli L, Pinchera A, Leoli F, Rago T, Bartolomei AM, Vitti P (1997) Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. J Clin Endocrinol Metab 82:1136–1139
10. International Council for Control of Iodine Deficiency disorders (2008) UNICEF REPORT 2008. In IDD Newsletter 30(4):1–20
11. Andersson M, Takkouche B, Egli I, Allen HE, de Benoist B (2005) Current global iodine status and progress over the last decade towards the elimination of iodine deficiency. Bull World Health Organ 83:518–525
12. Delange F (2007) Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition. Public Health Nutr 10:1571–1580; discussion 1581–1583
13. Becker DV, Braverman LE, Delange F, Dunn JT, Franklyn JA, Hollowell JG, Lamm SH, Mitchell ML, Pearce E, Robbins J, Rovet JF (2006) Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. Thyroid 16:949–951
14. WHO Secretariat, Andersson M, de Benoist B, Delange F, Zupan J (2007) Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr 10(12A):1606–1611
15. Zimmermann MB, Aeberli I, Torresani T, Burgi H (2005) Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study. Am J Clin Nutr 82:388–392
16. Zimmermann MB, Aeberli I, Andersson M, Assey V, Yorg JA, Jooste P, Jukic T, Kartono D, Kusic Z, Pretell E, San Luis TO Jr, Untoro J, Timmer A (2013) Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100–299 mug/L: a UNICEF/ICCIDD study group report. J Clin Endocrinol Metab 98:1271–1280
17. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Carle A, Pedersen IB, Rasmussen LB, Ovesen L, Jorgensen T (2009) Thyroglobulin as a marker of iodine nutrition status in the general population. Eur J Endocrinol 161:475–481
18. Zimmermann MB, Jooste PL, Pandav CS (2008) Iodine-deficiency disorders. Lancet 372:1251–1262
19. Zimmermann MB, Wegmuller R, Zeder C, Chaouki N, Torresani T (2004) The effects of vitamin A deficiency and vitamin A supplementation on thyroid function in goitrous children. J Clin Endocrinol Metab 89:5441–5447
20. Bernal J (2007) Thyroid hormone receptors in brain development and function. Nat Clin Pract Endocrinol Metab 3:249–259
21. Zoeller RT, Rovet J (2004) Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J Neuroendocrinol 16:809–818
22. Obregon MJ, Calvo RM, Del Rey FE, de Escobar GM (2007) Ontogenesis of thyroid function and interactions with maternal function. Endocr Dev 10:86–98
23. Auso E, Lavado-Autric R, Cuevas E, Del Rey FE, Morreale De Escobar G, Berbel P (2004) A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology 145:4037–4047
24. Cuevas E, Auso E, Telefont M, Morreale de Escobar G, Sotelo C, Berbel P (2005) Transient maternal hypothyroxinemia at onset of corticogenesis alters tangential migration of medial ganglionic eminence-derived neurons. Eur J Neurosci 22:541–551

25. Bernal J, Guadano-Ferraz A, Morte B (2003) Perspectives in the study of thyroid hormone action on brain development and function. Thyroid 13:1005–1012
26. McCarrison R (1909) Observations on endemic cretinism in the chitral and gilgit valleys. Proc R Soc Med 2:1–36
27. Boyages SC, Halpern JP, Maberly GF, Eastman CJ, Morris J, Collins J, Jupp JJ, Jin CE, Wang ZH, You CY (1988) A comparative study of neurological and myxedematous endemic cretinism in western China. J Clin Endocrinol Metab 67:1262–1271
28. Zimmermann MB, Kohrle J (2002) The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid 12:867–878
29. Cao XY, Jiang XM, Dou ZH, Rakeman MA, Zhang ML, O'Donnell K, Ma T, Amette K, DeLong N, DeLong GR (1994) Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med 331:1739–1744
30. Pharoah PO, Connolly KJ (1987) A controlled trial of iodinated oil for the prevention of endemic cretinism: a long-term follow-up. Int J Epidemiol 16:68–73
31. Qian M, Wang D, Watkins WE, Gebski V, Yan YQ, Li M, Chen ZP (2005) The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. Asia Pac J Clin Nutr 14:32–42
32. Lazarus JH (2014) Iodine status in Europe in 2014. Eur Thyroid J 3:3–6
33. Aghini Lombardi FA, Pinchera A, Antonangeli L, Rago T, Chiovato L, Bargagna S, Bertucelli B, Ferretti G, Sbrana B, Marcheschi M et al (1995) Mild iodine deficiency during fetal/neonatal life and neuropsychological impairment in Tuscany. J Endocrinol Invest 18:57–62
34. Vermiglio F, Sidoti M, Finocchiaro MD, Battiato S, Lo Presti VP, Benvenga S, Trimarchi F (1990) Defective neuromotor and cognitive ability in iodine-deficient schoolchildren of an endemic goiter region in Sicily. J Clin Endocrinol Metab 70:379–384
35. Zimmermann MB (2007) The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review. Thyroid 17:829–835
36. Romano R, Jannini EA, Pepe M, Grimaldi A, Olivieri M, Spennati P, Cappa F, D'Armiento M (1991) The effects of iodoprophylaxis on thyroid size during pregnancy. Am J Obstet Gynecol 164:482–485
37. Antonangeli L, Maccherini D, Cavaliere R, Di Giulio C, Reinhardt B, Pinchera A, Aghini-Lombardi F (2002) Comparison of two different doses of iodide in the prevention of gestational goiter in marginal iodine deficiency: a longitudinal study. Eur J Endocrinol 147:29–34
38. Soriguer F, Millon MC, Munoz R, Mancha I, Lopez Siguero JP, Martinez Aedo MJ, Gomez-Huelga R, Garriga MJ, Rojo-Martinez G, Esteva I, Tinahones FJ (2000) The auditory threshold in a school-age population is related to iodine intake and thyroid function. Thyroid 10:991–999
39. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341:549–555
40. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL (1999) Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 50:149–155
41. Lavado-Autric R, Auso E, Garcia-Velasco JV, Arufe Mdel C, Escobar del Rey F, Berbel P, Morreale de Escobar G (2003) Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. J Clin Invest 111:1073–1082
42. Berbel P, Mestre JL, Santamaria A, Palazon I, Franco A, Graells M, Gonzalez-Torga A, de Escobar GM (2009) Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid 19:511–519
43. Velasco I, Carreira M, Santiago P, Muela JA, Garcia-Fuentes E, Sanchez-Munoz B, Garriga MJ, Gonzalez-Fernandez MC, Rodriguez A, Caballero FF, Machado A, Gonzalez-Romero S, Anarte MT, Soriguer F (2009) Effect of iodine prophylaxis during pregnancy on neurocognitive

development of children during the first two years of life. J Clin Endocrinol Metab 94:3234–3241
44. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H (2010) Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 95:4227–4234
45. Chaouki ML, Benmiloud M (1994) Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. Eur J Endocrinol 130:547–551
46. Thilly C, Swennen B, Moreno-Reyes R et al (1994) Maternal, fetal and juvenile hypothyroidism, birthweight and infant mortality in the etiopathogenesis of the IDD spectrum in Zaire and Malawi. In: The damaged brain of iodine deficiency. Cognizant Communication Corporation, New York
47. DeLong GR, Leslie PW, Wang SH, Jiang XM, Zhang ML, Rakeman M, Jiang JY, Ma T, Cao XY (1997) Effect on infant mortality of iodination of irrigation water in a severely iodine-deficient area of China. Lancet 350:771–773
48. Bleichrodt N, Born M (1994) A metaanalysis of research on iodine and its relationship to cognitive development. In: The damaged brain of iodine deficiency. Cognizant Communication Corporation, New York, p 195
49. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 382:331–337
50. Santiago-Fernandez P, Torres-Barahona R, Muela-Martinez JA, Rojo-Martinez G, Garcia-Fuentes E, Garriga MJ, Leon AG, Soriguer F (2004) Intelligence quotient and iodine intake: a cross-sectional study in children. J Clin Endocrinol Metab 89:3851–3857
51. Hynes KL, Otahal P, Hay I, Burgess JR (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. J Clin Endocrinol Metab 98:1954–1962
52. van den Briel T, West CE, Bleichrodt N, van de Vijver FJ, Ategbo EA, Hautvast JG (2000) Improved iodine status is associated with improved mental performance of schoolchildren in Benin. Am J Clin Nutr 72:1179–1185
53. Zimmermann MB, Connolly K, Bozo M, Bridson J, Rohner F, Grimci L (2006) Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. Am J Clin Nutr 83:108–114
54. Crew MD, Spindler SR (1986) Thyroid hormone regulation of the transfected rat growth hormone promoter. J Biol Chem 261:5018–5022
55. Hochberg Z, Bick T, Harel Z (1990) Alterations of human growth hormone binding by rat liver membranes during hypo- and hyperthyroidism. Endocrinology 126:325–329
56. Miell JP, Zini M, Quin JD, Jones J, Portioli I, Valcavi R (1994) Reversible effects of cessation and recommencement of thyroxine treatment on insulin-like growth factors (IGFs) and IGF-binding proteins in patients with total thyroidectomy. J Clin Endocrinol Metab 79:1507–1512
57. Iglesias P, Bayon C, Mendez J, Gancedo PG, Grande C, Diez JJ (2001) Serum insulin-like growth factor type 1, insulin-like growth factor-binding protein-1, and insulin-like growth factor-binding protein-3 concentrations in patients with thyroid dysfunction. Thyroid 11:1043–1048
58. Zimmermann MB, Jooste PL, Mabapa NS, Mbhenyane X, Schoeman S, Biebinger R, Chaouki N, Bozo M, Grimci L, Bridson J (2007) Treatment of iodine deficiency in school-age children increases insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations and improves somatic growth. J Clin Endocrinol Metab 92:437–442
59. Biondi B, Cooper DS (2008) The clinical significance of subclinical thyroid dysfunction. Endocr Rev 29:76–131
60. Zimmermann MB, Aeberli I, Melse-Boonstra A, Grimci L, Bridson J, Chaouki N, Mbhenyane X, Jooste PL (2009) Iodine treatment in children with subclinical hypothyroidism due to

chronic iodine deficiency decreases thyrotropin and C-peptide concentrations and improves the lipid profile. Thyroid 19:1099–1104
61. Benmiloud M, Chaouki ML, Gutekunst R, Teichert HM, Wood WG, Dunn JT (1994) Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. J Clin Endocrinol Metab 79:20–24
62. Weng HX, Yan AL, Hong CL, Xie LL, Qin YC, Cheng CQ (2008) Uptake of different species of iodine by water spinach and its effect to growth. Biol Trace Elem Res 124:184–194
63. Tonacchera M, Dimida A, De Servi M, Frigeri M, Ferrarini E, De Marco G, Grasso L, Agretti P, Piaggi P, Aghini-Lombardi F, Perata P, Pinchera A, Vitti P (2013) Iodine fortification of vegetables improves human iodine nutrition: in vivo evidence for a new model of iodine prophylaxis. J Clin Endocrinol Metab 98:E694–E697
64. Sullivan KM, Perrine CG, Pearce EN, Caldwell KL (2013) Monitoring the iodine status of pregnant women in the United States. Thyroid 23:520–521
65. Martins MC, Lima N, Knobel M, Medeiros-Neto G (1989) Natural course of iodine-induced thyrotoxicosis (Jodbasedow) in endemic goiter area: a 5 year follow-up. J Endocrinol Invest 12:239–244
66. Pedersen IB, Laurberg P, Knudsen N, Jorgensen T, Perrild H, Ovesen L, Rasmussen LB (2007) An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. J Clin Endocrinol Metab 92:3122–3127
67. Wolff J, Chaikoff IL (1948) Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem 174:555–564
68. HaCPD-GSCoF EC (2002) Opinion of the Scientific Committee on Food on the tolerable upper level of intake of iodine. European Commission, Brussels