Introduction

Iodine is a micronutrient present in minute amounts (15–20 mg) in the human body, almost exclusively in the thyroid gland. Iodine is an essential component of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), comprising 65 and 59% of their respective weights. Thyroid hormones, and therefore iodine, are essential for mammalian life. They regulate many key biochemical reactions, especially protein synthesis and enzymatic activity. They also play a determining role in the process of early growth and development of most organs, especially that of the brain, which occurs in humans during the fetal and first 2–3 years of postnatal life. Consequently, iodine deficiency, if severe enough to affect thyroid hormone synthesis during this critical period, will result in hypothyroidism and brain damage. The clinical consequence will be irreversible mental retardation [1].

The recommended dietary intake of iodine has been discussed extensively elsewhere [2–4]. Table 1 compares the latest recommendations by the World Health Organization (WHO) in collaboration with the United Nation Children’s Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) [2], by the Institute of Medicine, National Academy of Sciences of the United States [3] and by the German ‘Arbeitskreis Jodmangel’ (National Iodine Committee of Germany, a European country previously affected by iodine deficiency). The recommendations by the two first groups are very similar except for infants aged less than 1 year and for pregnant and lactating women, for which the American recommendations are slightly higher than the ones by WHO/UNICEF/ICCIDD. Interestingly, the
German recommendations are the highest except for young infants for whom they are lower than the two first ones. These slight discrepancies are interesting because it is recognized that pregnant and lactating women and young infants are the most sensitive target groups for the effects of iodine deficiency.

When the physiological requirements of iodine have not been met in a given population, a series of functional and developmental abnormalities occur, including thyroid function abnormalities and, when iodine deficiency is severe, endemic goiter and cretinism, endemic mental retardation, decreased fertility rate, increased perinatal death and infant mortality. These complications, which constitute an hindrance to the development of the affected populations, are grouped under the general heading of iodine deficiency disorders (IDD) [5].

Iodine deficiency represents a major public health problem in the world as in 1990 (table 2) 1.6 billion individuals, i.e. 28.9% of the earth’s population, were at risk of iodine deficiency [6], and that 655 and 11.2 million individuals were affected by endemic goiter and endemic cretinism, respectively. All together, 43 million people were affected by several degrees of mental retardation due to iodine deficiency, which therefore appeared as the greatest single cause worldwide of preventable brain damage and mental retardation. Due to an improvement in the collection of data but in spite of the progress achieved during the past 10 years in the sustainable elimination of iodine deficiency, the figures were still higher in 1999 with 2.2 billion people at risk in 130 countries, i.e. 38% of the earth’s population, with 740 million people affected by goiter [2].

WHO/UNICEF/ICCIDD [2] have defined three levels of severity of iodine deficiency based on iodine intake: mild 50–99 μg/day; moderate 20–49 μg/day, and severe <20 μg/day.

---

### Table 1. Recommended dietary intakes of iodine (μg/day)

<table>
<thead>
<tr>
<th>Age groups/state</th>
<th>WHO/UNICEF/ICCIDD intake</th>
<th>US Academy of Sciences intake</th>
<th>Germany intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–59 months</td>
<td>90</td>
<td>0–12 months 110–130</td>
<td>0–12 months 50–80</td>
</tr>
<tr>
<td>6–12 years</td>
<td>120</td>
<td>1–8 years 90</td>
<td>1–9 years 100–140</td>
</tr>
<tr>
<td>Adolescents +</td>
<td>150</td>
<td>9–13 years 120</td>
<td>10 years through adulthood 180–200</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td>14–18 years 150</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>200</td>
<td>Adults 150</td>
<td>Pregnancy and lactation 230–260</td>
</tr>
<tr>
<td>Lactation</td>
<td>200</td>
<td>Pregnancy 220</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactation 290</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from WHO/UNICEF/ICCIDD [2] and the Institute of Medicine [3].
The aim of this chapter is to review, for each of these three levels of deficiency, the presently available data on the impact of iodine deficiency on thyroid function in pregnant women and their neonates and the possible long-term consequences of iodine deficiency occurring during the critical period of brain development on the neurointellectual development of infants and children. These two aspects are more extensively discussed elsewhere, as well as the potential repercussions of maternal, fetal and neonatal hypothyroxinemia due to iodine deficiency [1, 7].

The prevention and correction of iodine deficiency in the mother and infant will also be discussed.

### Iodine Deficiency and Thyroid Function during Pregnancy

In conditions of mild iodine deficiency [for review see, 8], the serum levels of free T4 steadily decrease during gestation, while in iodine sufficiency there is only a slight (15%) decrease by the end of gestation.

As a consequence, serum thyroid-stimulating hormone (TSH) levels increase progressively. This situation of chronic thyroid hyperstimulation results in an increase in serum thyroglobulin and in an increase in thyroid volume by 20–30% during gestation, a figure twice higher than in conditions of normal iodine supply.

In moderate iodine deficiency, the anomalies are of the same nature but more marked.

The few studies conducted in populations with severe iodine deficiency [for review see, 1] showed that the prevalence of goiter reaches peak values

<table>
<thead>
<tr>
<th>WHO regions</th>
<th>Total population millions</th>
<th>Population at risk of IDD millions</th>
<th>Population affected by goiter millions</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>550</td>
<td>181</td>
<td>86</td>
<td>15.6</td>
<td>32.8</td>
</tr>
<tr>
<td>Americas</td>
<td>727</td>
<td>168</td>
<td>63</td>
<td>8.7</td>
<td>23.1</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>406</td>
<td>173</td>
<td>93</td>
<td>22.9</td>
<td>42.6</td>
</tr>
<tr>
<td>Europe</td>
<td>847</td>
<td>141</td>
<td>97</td>
<td>11.4</td>
<td>16.7</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1,355</td>
<td>486</td>
<td>176</td>
<td>13.0</td>
<td>35.9</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1,553</td>
<td>423</td>
<td>141</td>
<td>9.0</td>
<td>27.2</td>
</tr>
<tr>
<td>Total</td>
<td>5,438</td>
<td>1,572</td>
<td>655</td>
<td>12.0</td>
<td>28.9</td>
</tr>
</tbody>
</table>

Adapted from WHO/UNICEF/ICCIDD [6].

1 Areas where the total goiter rate in school-aged children is equal to or greater than 5%.

### Table 2. Populations living in areas at risk of iodine deficiency disorders and affected by goiter in 1990

<table>
<thead>
<tr>
<th>WHO regions</th>
<th>Total population millions</th>
<th>Population at risk of IDD millions</th>
<th>Population affected by goiter millions</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
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<td>28.9</td>
</tr>
</tbody>
</table>
of up to 90% in females of child-bearing age (fig. 1) and that, during pregnancy, serum T4 is extremely low and serum TSH is extremely high. Comparative studies conducted in New Guinea and the Democratic Republic of Congo (DRC) showed that, in spite of the fact that the two areas are submitted to a similar degree of severe iodine deficiency (iodine intake <25 μg iodine/day), serum T4 in pregnant women is much higher in the DRC (103 nmol/l) than in New Guinea (38.6–64.4 nmol/l). This discrepancy was understood only when it was demonstrated that in the DRC, iodine deficiency is aggravated by selenium deficiency and thiocyanate overload (see below).

## Iodine Deficiency and Neonatal Thyroid Function

In mild iodine deficiency, the serum concentrations of TSH and thyroglobulin are still higher in neonates than in their mothers [for reviews see, 1, 7, 9, 10]. The frequency distribution of neonatal TSH on day 5, at the time of systematic screening for congenital hypothyroidism, is shifted towards elevated values. The frequency of values above 5 mU/l blood is 4.5%, while the normal value is <3% [6, 10].

In moderate iodine deficiency, the anomalies are of the same nature but more drastic. The frequency of a neonatal TSH above 20–25 mU/l blood that is above the cutoff point used for recalling neonates due to suspicion of congenital hypothyroidism in programs of systematic screening for
congenital hypothyroidism, is increased. This frequency is inversely related to the median urinary iodine of populations of neonates used as an index of their iodine intake. In addition, transient neonatal hypothyroidism can occur with a frequency approximately 6 times higher in Europe than in the United States, where the iodine intake is much higher.

In severe iodine deficiency, as in the mothers, the biochemical picture of neonatal hypothyroidism is caricatural. In the DRC, as many as 11% of the neonates have both a cord serum TSH of >100 mU/ml and a cord T4 of <38.6 nmol/l, i.e. a biochemical picture similar to that found in thyroid agenesis.

The changes in neonatal TSH and thyroid function in the neonates in all conditions of iodine deficiency are much more frequent and severe than in their mothers. The hypersensitivity of neonates to iodine deficiency is explained by their very small intrathyroidal iodine pool, which requires increased TSH stimulation and a fast turnover rate in order to maintain a normal secretion of thyroid hormones.

### Iodine Deficiency during the First Months of Life

Contrasting with the abundance of data on the consequences of iodine deficiency on thyroid function during pregnancy, in the neonate, as well as in children and adults, there are few data on the impact of the deficiency on thyroid function in the young infant.

In conditions of mild iodine deficiency, as indicated earlier, the frequency distribution of neonatal TSH is shifted towards elevated values and the frequency of transient hyperthyrotropinemia and transient primary hypothyroidism is much higher than in iodine replete areas [for review see, 11]. In particular, thyroid function of preterm infants is characterized by a biochemical picture including low total and free T4, elevated TSH and exaggerated TSH response to TRH. This picture of primary subclinical hypothyroidism is in contrast with the picture of tertiary hypothyroidism evidenced in preterm infants in iodine replete areas, characterized by the fact that TSH remains normal in spite of low free T4.

In conditions of severe iodine deficiency, the data in infants are still more scanty: in the DRC, it was found that the frequency of biochemical signs of congenital hypothyroidism (9.0%) was as frequent in infants aged 5 days as in neonates [12]. Follow-up studies showed that in some of these infants, the signs spontaneously corrected within a few weeks. The transient character of hypothyroidism in some of these infants may explain why the incidence of congenital hypothyroidism (close to 10%) is almost ten times higher than the prevalence of myxedematous endemic cretinism in the general population of the Ubangi area (1%). Another factor could be the high mortality rate of hypothyroid newborns and young infants [13]. The hypothesis was proposed
that transient neonatal and infantile hypothyroidism in the DRC resulted in endemic mental retardation while permanent hypothyroidism occurring during this critical period resulted in the long-term development of endemic cretinism [14].

**Iodine Deficiency and Neurointellectual Development**

As indicated earlier, iodine deficiency occurring during the critical period of brain development can result in brain damage and is the leading cause of preventable, irreversible mental retardation.

The data summarized in table 3 strongly suggest that mild and moderate iodine deficiency affects the intellectual development of the children. The psychometric tests used to evidence these abnormalities include locally adapted ‘culture-free’ intelligence tests. The findings include low visual-motor performances, motor skill, perceptual and neuromotor abilities and low development and intellectual quotients (IQs).

In severe iodine deficiency, the anomalies found in the ‘normal population’ are of the same type, although more frequent and more severe than the ones found in moderate iodine deficiency. The frequency distribution of the IQs is shifted towards low values as compared with matched controls who were not exposed to iodine deficiency during the critical period of brain development because of correction of the deficiency in the mothers before or during early gestation. In their meta-analysis of 19 studies on neuromotor and cognitive functions in conditions of severe iodine deficiency, Bleichrodt and Born [15] concluded that iodine deficiency results in a loss of 13.5 IQ points at the level of the global population.

The most dramatic consequence of iodine deficiency on brain and physical development is endemic cretinism [16]. Endemic cretinism is a polymorphous clinical entity defined essentially by severe and irreversible alterations in brain development, mental retardation and a combination of neurological signs including deafmutism, squint, spastic diplegia, motor rigidity, shuffling gait and of signs of severe thyroid insufficiency with dwarfism, myxedema and sexual immaturity. The prevalence of cretinism can be as high as 15% of the population and this condition constitutes an hindrance to the socioeconomic development of populations exposed to iodine deficiency.

**Mechanisms of Brain Damage due to Iodine Deficiency during the Perinatal Period**

The spectrum of the defects in brain development and neurointellectual performances resulting from iodine deficiency have to be interpreted on the basis of two recent sets of findings [for reviews see, 1, 7, 16].
<table>
<thead>
<tr>
<th>Regions</th>
<th>Tests</th>
<th>Findings</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>Locally adapted Bayley McCarthy Cattell</td>
<td>Lower psychomotor and mental development than controls</td>
<td>Bleichrodt et al. [22], 1989</td>
</tr>
<tr>
<td>Italy</td>
<td>Sicily Bender-Gestalt</td>
<td>Low perceptual integrative motor ability Neuromuscular and neurosensorial abnormalities</td>
<td>Vermiglio et al. [23], 1990</td>
</tr>
<tr>
<td></td>
<td>Tuscany Wechsler Raven</td>
<td>Low verbal IQ, perception, motor and attentive functions</td>
<td>Fenzi et al. [24], 1990</td>
</tr>
<tr>
<td></td>
<td>Tuscany Wisc Reaction time</td>
<td>Lower velocity of motor response to visual stimuli</td>
<td>Vitti et al. [25], 1992 Aghini-Lombardi et al. [26], 1995</td>
</tr>
<tr>
<td>India</td>
<td>Verbal, pictorial learning tests Tests of motivation</td>
<td>Lower learning capacities</td>
<td>Tiwari et al. [27], 1996</td>
</tr>
<tr>
<td>Iran</td>
<td>Bender-Gestalt Raven</td>
<td>Retardation in psychomotor development</td>
<td>Azizi et al. [28], 1993</td>
</tr>
<tr>
<td>Malawi</td>
<td>Psychometric tests including verbal fluency</td>
<td>Loss of 10 IQ points as compared to iodine-supplemented controls</td>
<td>Shrestha [29], 1994</td>
</tr>
<tr>
<td>Benin</td>
<td>Battery of 8 nonverbal tests exploring fluid intelligence and 2 psychomotor tests</td>
<td>Loss of 5 IQ points as compared to controls supplemented with iodine for 1 year</td>
<td>van den Briel et al. [30], 2000</td>
</tr>
</tbody>
</table>
Roles of Maternal, Fetal and Neonatal Hypothyroxinemia

Mental retardation and endemic cretinism result from an insufficient supply of thyroid hormones to the developing brain. The action of thyroid hormone is exerted through the binding of T3 to nuclear receptors which regulate the expression of specific genes in different brain regions following a precise development schedule. During fetal and early postnatal life, T3 bound to the nuclear receptors is entirely dependent on its local production from T4 via type-II deiodinase (D2) and is not related to the serum level of T3.

A key issue is that recent experimental and clinical data have underlined the importance of the transfer of thyroid hormones across the placenta even during early gestation, contrasting with the former dogma that this transfer is extremely limited: in the rat, thyroid hormones are found in embryonic and fetal tissues before the onset of fetal thyroid function which occurs on day 18 of gestation. Nuclear receptors to T3 are present in the fetal brain by 14 days of gestation, also before the onset of fetal thyroid function. At that stage, the T4 and T3 available to embryos and fetuses are of maternal origin. At term, 17.5% of fetal extrathyroidal T4 is still of maternal origin. These data extend the period of sensitivity of the brain to thyroid hormones well into early phases of gestation when the supply of these hormones is entirely of maternal origin.

Similarly, in humans, T4 is already found in the first trimester coelomic fluid from the 6th week of gestational age, a long time before the onset of fetal thyroid function, which occurs at the 24th week of gestation. The number of T3 receptors and the amount of T3 bound to the receptors in the whole brain increase about 10-fold between 10 and 18 weeks, also before the onset of fetal thyroid function. At term, about 20–50% of cord serum T4 is still of maternal origin.

These data underline the importance of maternal thyroxinemia for the availability of thyroid hormones to the developing brain of the fetus. They explain that brain damage in severe iodine deficiency is much more severe than brain damage caused by sporadic congenital hypothyroidism: in the latter condition, maternal thyroxinemia is normal and fetal serum T4 of maternal origin is able to protect the fetal brain during early fetal life.

Additional Roles of Selenium Deficiency and Thiocyanate Overload

Selenium is present in high concentrations in the normal thyroid. It is present in glutathione peroxidase and superoxide dismutase, the enzymes responsible for the detoxification of toxic derivatives of oxygen (H₂O₂ and perhaps O₂⁻). Selenium is also present in the type-I iodothyronine 5'-deiodinase responsible for the peripheral conversion of T4 to T3.

The following scheme has been proposed to explain the influence of selenium deficiency on thyroid function and brain development in the fetus in the presence of iodine deficiency: iodine deficiency results in hyperstimulation of the thyroid by TSH and consequently in increased production of H₂O₂ within the cells. Selenium deficiency results in glutathione peroxidase deficit and
consequently in accumulation of $H_2O_2$. Excess $H_2O_2$ could induce thyroid cell destruction and finally thyroid fibrosis, resulting in thyroid failure. On the other hand, deficiency in iodothyronine 5'-deiodinase in pregnant mothers induced by selenium deficiency causes decreased catabolism of T4 to T3 and thus increased availability of maternal T4 for the fetus and its brain.

This scheme explains why in situations characterized by isolated severe iodine deficiency such as New Guinea, China, Indonesia and Thailand, the clinical picture of endemic cretinism is characterized by a dominant neurological picture and why, when selenium deficiency and thiocyanate overload are added, as in the DRC, the neurologic signs are mitigated and the picture is dominated by severe hypothyroidism.

The role of thiocyanate in the etiology of endemic cretinism in Africa has been proposed because of the observation that people in areas with severe uniform iodine deficiency exhibit cretinism only when a certain critical threshold level in the dietary supply of thiocyanate is reached. The action of thiocyanate is entirely due to an aggravation of iodine deficiency resulting in fetal hypothyroidism.

**Prevention and Correction of Iodine Deficiency in Mother and Infant**

All disorders induced by iodine deficiency in all age groups including young infants can be prevented by the correction of iodine deficiency in the affected populations. Many approaches to the correction of iodine deficiency have been used and their description and discussion are outside the scope of the present paper. They are summarized elsewhere in publications by the United Nations Agencies [2, 6], by nongovernmental organizations such as the ICCIDD [17] and by individual authors [18]. The possibility of correcting iodine deficiency at low cost has been the starting point of massive campaigns of prevention of IDD based on food fortification and especially based on universal salt iodination, that is iodination of all human and livestock salt, including salt used in the food industry. Enormous investments have been made in the implementation and monitoring of programs of salt iodination around the world. Thanks to a remarkable collaboration between all stakeholders, including the governments and populations of the affected countries, health professionals including nutritionists, endocrinologists and epidemiologists, the salt industry and major donors including UN agencies (UNICEF, WHO, World Bank), Kiwanis International and bilaterals, during the last 10 years in the 130 countries affected by IDD the percentage of households consuming iodized salt has increased from less than 10% in 1990 to 68% in 1999 [2, 17, 18]. At the same time, 75% of these countries implemented legislation on salt iodination, 73 and 61% had programs for monitoring the quality of salt and the iodine status, respectively. This represents an unprecedented success in the field of prevention of non-communicable diseases and especially of micronutrient deficiencies. Other
programs of food fortification exist for iodine fortification of bread, water and even sugar [19].

However, these programs of food fortification have no direct effect on young infants and even on pregnant and lactating women because these age groups are recommended to limit their intake of salt. In order to have a positive impact on the iodine nutrition of young infants, the access to food fortified with iodine, essentially iodized salt, has to be organized before the initiation of pregnancy.

During pregnancy, lactation and early infancy, iodine supplementation remains the most efficient way to prevent the development of IDD.

In conditions of extreme iodine deficiency in areas with endemic goiter and cretinism, large campaigns for iodine supplementation with the administration of iodized oil have been organized with a remarkable success and absence of side effects in the prevention of maternal, fetal and neonatal hypothyroidism and brain damage [20].

In areas with mild to moderate iodine deficiency, essentially western Europe, iodine supplementation rather than food fortification has to be organized during pregnancy, lactation and early infancy. Physiological quantities of iodine have been included in the multivitamin tablets for pregnant and lactating women. Such supplements, when required, should optimize the iodine content of breast milk to values varying between 130 and 180μg/l [21]. Similarly, in order to achieve a positive balance which is required for growing infants, the iodine content of formula milk should be at least 10μg/dl for the full-term and 20μg/l for the preterm infants [4]. After weaning, daily supplements of some 90–100μg/day are recommended for infants and children up to the end of brain development, that is up to 2–3 years of age.

**Conclusion**

The main impact of iodine deficiency on humans is much more on the brain than on the thyroid. The interrelationship between thyroid function in the mother and infant has been demonstrated as well as the critical role of maternal thyroxinemia during the whole gestation, including the early stage, on the future neurointellectual development of the progeny. Brain damage to the developing child is entirely preventable by correction of iodine deficiency implemented during early gestation, ideally even before the initiation of the gestation.

Additional research is still needed at least on the three following aspects.

1. Adequacy of iodine nutrition during pregnancy: discrepancies exist between the recommendations on dietary intake during pregnancy. If there is a global agreement that, in nonpregnant adults and adolescents, adequate iodine nutrition is indicated by a median urinary iodine concentration of between 100 and 200μg/l in representative samples of the populations, the corresponding criterion has not been established during pregnancy.
Evaluation of the degree of retardation in neurointellectual development in mild iodine deficiency: additional data are required in order to confirm that even mild iodine deficiency results in irreversible brain damage. This point is particularly important because it represents one of the major reasons why public health measures aiming at increasing the iodine intake of populations should be implemented even in the case of mild iodine deficiency, as presently evidenced in many European countries.

Public health measures aiming at the correction of iodine deficiency in mothers and infants: iodination of salt, which is so efficient for children, adolescents and adults, is of limited value for pregnant and lactating women and for infants and children before weaning because of the recommended limited access of these age groups to salt. Other types of food fortification or supplementation with iodine have to be more precisely defined and implemented in these 2 age groups, which are precisely the most sensitive to the effects of iodine deficiency.

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Iodine Deficiency Disorders

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Discussion

Dr. Pettifor: Do you have any evidence that children or infants who are breast-fed by mothers who have low breast milk iodine levels have elevated thyroid-stimulating hormone (TSH)? In other words during this period that they are exclusively breast-fed, do they run the risk of becoming hypothyroid?

Dr. Delange: Yes, they do have elevated TSH and persisting elevated TSH [1]. This means that they are at risk of brain damage. Consequently, the mothers and the infants themselves should be supplemented with iodine.

Dr. Endres: In the 9 cases from Sicily you cited with transient hypothyroidism, were they term or preterm infants?

Dr. Delange: These were full-term infants.

Dr. Azizi: I should add that in addition to the 9 children that Dr. Delange mentioned from Sicily, about 2 years ago we also published a study on another 14 children who had a transient increase in TSH and were completely normal after the 3rd month of
life, and then between 4 and 6 years of age they had a much lower IQ than normal children [2]. So it is true that a transient increase in TSH will decrease the IQ.

**Dr. Endres:** In order to avoid brain damage, should we use a lower cutoff level for TSH in the screening and should we systematically supplement preterm infants with thyroxine (T₄)?

**Dr. Delange:** Decreasing the cutoff point would unnecessarily increase the recall rate as in iodine-replete populations, less than 3% of the neonates have a blood TSH above 5 mU/l blood. There is no evidence after careful well-controlled studies that long-term therapy with T₄ is really indicated in preterm infants of less than 30 weeks of gestation [3].

**Dr. West:** In a couple of your graphs I saw a peak of TSH immediately after birth. Is it a true physiological peak and, if not, can you link that to the IQ loss in transient neonatal hypothyroidism?

**Dr. Delange:** This TSH surge, as it is usually called, that is this transiently elevated TSH found during the first 24 h of life, is considered to be entirely physiological. Now how do you define physiology? This means that you find this in populations where there is no iodine deficiency. The mechanism is not entirely elucidated. It is at least partly due to the cooling of the neonate immediately after birth and to the cutting of the cord. So it is not a response to a decrease in the free fraction of thyroid hormones through the usual feed back. In other words, it is not considered an indicator of possible brain damage.

**Dr. Azizi:** This is why we have two kinds of normal levels. If the blood sample is collected right after birth or from the cord, the cutoff point is above 20 mU/l; however, if you take it as a usual screening test 3 days after birth, the cutoff point will be about 5 mU/l as Dr. Delange mentioned. So we have two different types of normal levels.

**Dr. Young:** You indicated that the mechanism behind the mental retardation in iodine deficiency isn't known, but you did indicate that iodine deficiency is associated with an apparent delay in synaptic development. In view of the public health significance of iodine deficiency, it surprises me that so little has been done to identify the genes and the signaling pathways that might be involved in this particular context, or is this being undertaken at the moment? How does the application of genomic techniques and microarray analysis of one kind or another measurably help us to understand the mechanism and reduce this gap in our ignorance in this context?

**Dr. Delange:** The molecular basis for mental retardation is largely known. There are conventions of neuroscience and neurobiology which perfectly indicate what kind of processes are impaired when there is an insufficient quantity of thyroid hormones [4]. I think this is largely known, and at least sufficiently and clearly enough to indicate that when simplistic indicators, such as low urinary iodine and elevated frequency of goiter which were selected on purpose by the public health organizations, are abnormal, action is required.

**Dr. Azizi:** The idea of having more genetic and molecular biology work in iodine deficiency disorder is very interesting because even in villages with severe iodine deficiency, not all the people are affected. You can find 50% of them severely affected and 50% with much milder consequences. So in addition to the environmental factor, which is strong, there must be some genetic and molecular susceptibility or resistance.

**Dr. Al Frayh:** Is there any upper limit to iodine fortification in food? In other words are there any long-term longitudinal studies on over-fortification? When you have an excess of iodine in nutrition, are there any negative consequences on human subjects? I am looking at it not just from a theoretical point of view, but if there is no legislative regulation on the fortification of foods with iodine you may have a risk of over-fortification. I am just asking whether any long-term negative effects of excessive iodine consumption exist?
Dr. Delange: This is a very critical question. The answer is yes, there are side effects to iodine excess. The safe upper limit of iodine intake varies from one population to the other. In other words there is not one absolute figure which is the upper limit of normal. It is usual to consider that normal adults will tolerate up to 1,000 μg iodine/day. Now if you administer 1,000 μg iodine/day to adults in say, North America where there is a long history of normal iodine nutrition, nothing will happen. If you do this in a population which used to be iodine deficient in the past, there is a real danger that you will induce new diseases due to iodine excess such as hyperthyroidism, that is iodine-induced hyperthyroidism and thyroid autoimmunity [5]. The hyperthyroidism induced by iodine supplementation in iodine-deficient areas is due to the fact that long-standing iodine deficiency results in the development of nodules in the thyroid gland which loose their control towards an excess of iodine and which very unfortunately have the characteristics to produce as much thyroid hormones as they receive iodine. This means that if they receive too much iodine they produce too many hormones. There have been cases, especially in Central Africa, where there were real epidemics of hyperthyroidism which were occasionally lethal [6]. So the problem of the upper limit is a very touchy figure. This is why I am personally not pleased by the recommendation that the level of salt iodination should be at least so and so, usually 15 parts per million. An upper limit has to be given as well and this upper limit will depend on the past history of the country. In other words iodine supplementation has dangers of inducing side effects, but it is properly and universally recognized that the benefits of iodine supplementation by-and-large outweigh the disadvantages [5, 7].

Dr. Beard: I simply wanted to ask if the transitory hypothyroidism in early pregnancy has ever been related to transitory zinc deficiency, iron deficiency and perhaps vitamin A deficiency, because certainly the animal model and a few human studies have shown an interrelationship, and you can probably throw selenium in there as well.

Dr. Delange: I think that is an excellent question as we know that iron deficiency diminishes the bioavailability of iodine [8]. However, there is no evidence of such a phenomenon in the etiology of transient neonatal hypothyroidism. This interaction between different micronutrients definitely needs a more careful approach.

Dr. Allen: Mine was the same question.

References


