Introduction

Iodine is a micronutrient present in the human body in minute amounts (15-20 mg), almost exclusively in the thyroid gland. Iodine is an essential component of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), comprising 65 and 59 percent of their respective weights. Thyroid hormones, and therefore iodine, 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 two to three 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 dietary intake of iodine recommended by the World Health Organization (WHO), the United Nation Children’s Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) (2), are 90 µg per day from 0 to 59 months, 120 µg/d from 6 to 12 years, 150 µg/d for adolescents and non pregnant adults and 200µg/d during pregnancy and lactation (2).

When these physiological requirements are not 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 a hindrance to the development of the affected populations, are grouped under the general heading of Iodine Deficiency Disorders, IDD (3).

Iodine deficiency represents a major public health problem in the world as in 1990, 1.6 billion individuals, i.e. 28.9 % of the earth population, were at risk of iodine deficiency and as 655 and 11.2 million individuals were affected by endemic goiter and by 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 (4). Due to an improvement in the collection of data and in spite of the progress achieved during the past ten 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 population, with 740 million people affected by goiter (2).
WHO/UNICEF/ICCIDD (2) has defined three levels of severity of iodine deficiency based on iodine intake as follows: mild: 50-99 µg/day; moderate: 20-49 µg/day; severe: < 20 µg/day.

The aim of the present paper is to review, for each of these three levels of deficiency, presently available data on the impact of iodine deficiency on thyroid function in pregnant women and their progeny and on the possible longterm 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 (1, 5).

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

I. Iodine deficiency and thyroid function during pregnancy

In conditions of mild iodine deficiency (review in ref. 6), 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 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 (Review in ref. 1) showed that the prevalence of goiter reaches peak values of up to 90 % in females of child bearing age 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 below 25 µg iodine/d), 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 DRC, iodine deficiency is aggravated by selenium deficiency and thiocyanate overload (See section VI 2).

II. Iodine deficiency and neonatal thyroid function (Reviews in refs. 1, 5, 7, 8).

In mild iodine deficiency, the serum concentrations of TSH and thyroglobulin are still higher in neonates than in their mothers. 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 below 3 % (4, 8).

In moderate iodine deficiency, the anomalies are of the same nature but more drastic. The frequency of neonatal TSH above 20-25 mU/l blood, that is
above the cut-off point used for recalling the neonates because of 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, the biochemical picture of neonatal hypothyroidism is caricatural. In the DRC, as many as 11% of the neonates have both a cord serum TSH above 100 mU/ml and a cord T4 below 38.6 nmol/l, i.e. a biochemical picture similar to the one 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.

III. Iodine deficiency in early infancy

Contrasting with the abundance of data on the consequences of iodine deficiency on thyroid function during pregnancy, in the neonate and in 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 (Review in ref. 9). 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 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 (10). 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 (11). The hypothesis was proposed that transient neonatal and infantile hypothyroidism in DRC resulted in endemic
mental retardation while permanent hypothyroidism occurring during this critical period resulted in the longterm development of endemic cretinism (12).

IV. Iodine deficiency in childhood and adolescence

The view that endemic goiter constitutes the most efficient mechanism of adaptation to iodine deficiency is based, with a few exceptions (Review in ref. 12) on information available only in adults. But a study of the time course as a function of age from 3 to 22 years of the main variables exploring thyroid function in two populations submitted to a similar degree of iodine deficiency but with markedly different prevalences of goiter showed that goiter constitutes, rather, an unfavorable side effect to the mechanism of adaptation to iodine deficiency which is increased trapping of iodide by the thyroid, as indicated by an elevated thyroidal uptake of radioiodine (12). It was also shown that the highest values of serum TSH were observed in the youngest infants and children in spite of the fact that they had also the highest serum T4 values. These variations of the TSH/T4 ratio as a function of age could reflect the increase with age of the iodine content of the thyroid and/or changes in the sensitivity of the thyroid to TSH (12).

V. 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.

Mild and moderate iodine deficiency both 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 (IQ).

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 IQ 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 (13) concluded that severe 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 (14). 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.

VI. 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 (Reviews in refs. 1, 5, 14. See also review by Bernal in this issue):

1. Roles of maternal, fetal and neonatal hypothyroxinemia

Mental retardation and endemic cretinism result from an insufficient supply of thyroid hormones to the developing brain.

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 receptor 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 to 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 fetal brain during early fetal life.

2. Additional roles of selenium deficiency and thiocyanate overload

Selenium is present in high concentrations in the normal thyroid. It is present in glutathione peroxydase (Gpx) and superoxide dismutase, the enzymes responsible for the detoxification of toxic derivatives of oxygen (H$_2$O$_2$).
and perhaps $O_2^-$. Selenium is also present in the type I iodothyronine 5'-deiodinase responsible for the peripheral conversion of T4 to T3.

A scheme has been proposed, as follows, for explaining 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 $H_2O_2$ within the cells. Selenium deficiency results in Gpx 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 level threshold 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.

**VII. 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 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, 4), by non governmental organizations such as the International Council for Control of Iodine Deficiency Disorders (ICCIDD) (15) and by individual authors (16). The possibility to correct 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 Iodization, that is iodization 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 iodization around the world. During the last ten years, and 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, the percentage of the 130 countries...
affected by IDD with 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 legislations on salt iodization; 73 and 61 % had programs for monitoring the quality of salt and the iodine status of the populations respectively. This represents an unprecedent 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 (17).

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 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 iodine deficiency disorders.

In conditions of extreme iodine deficiency in areas with endemic goiter and cretinism, large campaigns of iodine supplementation by 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 (18).

In areas with mild to moderate iodine deficiency, essentially Western Europe, iodine supplementation in addition to food fortification has to be organized during pregnancy, lactation and early infancy. Physiological quantities of iodine have been included to the multivitamins tablets for pregnant and lactating women. Such supplements, when required, should optimize the iodine content of breastmilk to values varying between 130 an 180 µg/l (19). Similarly, in order to achieve the positive iodine balance which is required for the growing infants, the iodine content of formula milk should be at least 10 µg/dl for the fullterms and 20 µg/l for the preterms (20). After weaning, daily supplements of some 90 to 100 µg/day are recommended for infants and children up to the end of brain development, that is up to two to three years of age.

VIII. 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 mother and infant has been demonstrated as well as the critical role of maternal thyroxinemia during the whole gestation, including during its 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:

a) Adequacy of iodine nutrition during pregnancy: discrepancies exist between the recommendations on dietary intake during pregnancy. If there is a global agreement that in non pregnant adults and adolescents, adequate iodine nutrition is indicated by a median urinary iodine concentration between 100 and 200 µg/l in representative samples of the populations (2), the corresponding criterion is not established during pregnancy. A recent WHO consultation on this topic (in press) should further clarify the situation.

b) 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.

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


