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## Editorial

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### Iodine deficiency as a cause of brain damage

#### Abstract

**This editorial reviews the impact of iodine deficiency (1) on thyroid function in pregnant women and neonates and (2) on the neurointellectual development of infants and children.**

**All degrees of iodine deficiency (mild: iodine intake of 50–99 µg/day, moderate: 20–49 µg/day, and severe: <20 µg/day) affect thyroid function of the mother and the neonate as well as the mental development of the child. The damage increases with the degree of the deficiency, with overt endemic cretinism as the severest consequence. Maternal hypothyroxinaemia during early pregnancy is a key factor in the development of the neurological damage in the cretin. Selenium deficiency combined with iodine deficiency partly prevents the neurological damage but precipitates severe hypothyroidism in cretins.**

**Iodine deficiency results in a global loss of 10–15 IQ points at a population level and constitutes the world's greatest single cause of preventable brain damage and mental retardation.**

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Children born in iodine deficient areas are at risk of neurological disorders and mental retardation because of the combined effects of maternal, fetal, and neonatal hypothyroxinaemia.<sup>1</sup> The reasons are that iodine is required for the synthesis of thyroid hormones and that thyroid hormones, in turn, act by regulating the metabolic pattern of most cells of the organism. They also play a determining part in the process of early growth and development of most organs, especially of the brain,<sup>2–4</sup> which occurs in humans during fetal and early 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 mental retardation.

The recommended dietary allowance of iodine is 50 µg/day from 0 to 6 months, 90 µg/day from 6 months to 6 years, 120 µg/day from 7 to 10 years, 150 µg/day during adolescence and adulthood, and 200–300 µg/day during pregnancy and lactation.<sup>5</sup> When these physiological requirements are not met in a given population, a series of functional and developmental abnormalities occur, includ-

ing thyroid function abnormalities and, when iodine deficiency is severe, endemic goitre 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.<sup>6</sup>

In 1990, 1.6 billion people, that is 28.9% of the earth's population, were at risk of iodine deficiency,<sup>7</sup> which therefore appeared as the world greatest single cause of preventable brain damage and mental retardation.

The World Health Organisation (WHO), the United Nations Children's Fund (Unicef), and the International Council for Control for Iodine Deficiency Disorders (ICCIDD) have defined three degrees of severity of iodine deficiency: mild (iodine intake of 50–99 µg/day), moderate (20–49 µg/day), and severe (<20 µg/day).<sup>7</sup>

The aim of this editorial is to review, for each of these three degrees of deficiency, presently available data on: (1) the impact of iodine deficiency on thyroid function in pregnant women and their neonates and (2) the possible long term consequences of iodine deficiency occurring during the critical period of brain development on the neurointellectual development of infants and children.

Extensive reviews on these different aspects are available elsewhere.<sup>1 8–12</sup>

#### Thyroid function during pregnancy and iodine deficiency

Glinoer and his group showed that, in conditions of mild iodine deficiency, the serum concentrations of free thyroxine decrease steadily and significantly during gestation.<sup>9 13</sup> Although the median values remain within the normal range, one third of pregnant women have free thyroxine values near or below the lower limit of normal. This picture is in clear contrast with thyroid status during normal pregnancy and normal iodine intake, which is characterised by only a slight (15%) decrease of free thyroxine by the end of gestation.

After an initial blunting of serum thyroid stimulating hormone (TSH) caused by increased concentrations of human chorionic gonadotrophin, serum TSH concentrations increase progressively in more than 80% of pregnant Belgian women, although these levels also remain within the normal range. This change is accompanied by an increase in serum thyroglobulin, which is directly related to the increase in TSH.

This situation of chronic thyroid hyperstimulation results in an increase in thyroid volume by 20% to 30% during gestation, a figure twice as high as that in conditions of normal iodine supply.

The role of the lack of iodine in the development of these different anomalies is indicated by the fact that a daily supplementation with physiological doses of iodine (150 µg/day) prevents their occurrence.<sup>14</sup>

In moderate iodine deficiency, the anomalies are of the same nature but more marked. For example, in an area of Sicily with an iodine intake of 40 µg/day, Vermiglio *et al* reported a decline of serum free thyroxine of 31% and a simultaneous increase of serum TSH of 50% during early (8th to 19th weeks) gestation.<sup>15</sup>

Only a limited number of studies are available on thyroid function during pregnancy in populations with severe iodine deficiency (iodine intake below 25 µg iodine/day). Moreover, because of the extremely difficult conditions in which these studies were performed, the results are necessarily only partial. The most extensive data are available from New Guinea<sup>16, 17</sup> and the Democratic Republic of Congo (DRC, formerly Zaire).<sup>18, 19</sup>

The studies conducted in such environments show that the prevalence of goitre reaches peak values of up to 90% in females of child bearing age<sup>20</sup> and that during pregnancy, serum thyroxine is extremely low and serum TSH extremely high. However, it has been pointed out that for a similar degree of severe iodine deficiency in the DRC and New Guinea, serum thyroxine in pregnant mothers is much higher in the DRC (103 nmol/l) than in New Guinea (38.6–64.4 nmol/l).<sup>21</sup> The frequency of values below 32.2 nmol/l is only 3% in the DRC while it is 20% in New Guinea. This discrepancy was understood only when it was demonstrated that in the DRC iodine deficiency is aggravated by selenium deficiency and thiocyanate overload (see later section).<sup>19, 22, 23</sup>

### Neonatal thyroid function in iodine deficiency

In mild iodine deficiency serum concentrations of TSH and thyroglobulin are still higher in neonates than in mothers,<sup>9, 13</sup> indicating that neonates are more sensitive than adults to the effects of iodine deficiency. Again, the role of iodine deficiency is demonstrated by the fact that neonates born to mothers who have been supplemented with iodine during pregnancy have a lower thyroid volume and serum thyroglobulin and higher urinary iodine than newborns born to untreated mothers.<sup>14</sup>

Other evidence of chronic TSH overstimulation of the neonatal thyroid is the fact that there is a slight shift towards increased values of the frequency distribution of neonatal TSH on day 5, which is the time of systematic screening for congenital hypothyroidism. The frequency of values above 5 mU/l blood is 4.5%, while the normal value is below 3%.<sup>24</sup>

In moderate iodine deficiency, the anomalies are of the same nature but more drastic than in conditions of mild iodine deficiency. Transient hyperthyrotrophinaemia or even transient neonatal hypothyroidism can occur. The frequency of the latter condition is approximately six times higher in Europe than in the United States where the iodine intake is much higher.<sup>25</sup>

The shift of neonatal TSH towards increased values is more marked and the frequency of values 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 programmes of systematic screening for congenital hypothyroidism, is increased. There is an inverse relationship between the median urinary iodine of populations of neonates used as an index of their iodine intake and the recall rate at screening.<sup>20, 24</sup>

It has to be pointed out that these changes in neonatal TSH frequently occur for levels of iodine deficiency that would not affect the thyroid function in non-pregnant adults. The hypersensitivity of neonates to the effects of 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 normal secretion of thyroid hormones.<sup>24, 26</sup>

In severe iodine deficiency, as in the mothers, the biochemical picture of neonatal hypothyroidism is caricatural, especially in the DRC where mean cord serum thyroxine and TSH concentrations are 95.2 nmol/l and 70.7 mU/l respectively and where as many as 11% of the neonates have both a cord serum TSH above 100 mU/l and a cord thyroxine below 38.6 nmol/l, that is a biochemical picture similar to the one found in thyroid agenesis.<sup>19, 26</sup>

### Neurointellectual development in iodine deficiency

There is no evidence that the minor impairment of thyroid function evidenced in mothers and neonates in conditions of mild iodine deficiency clearly affects the intellectual development of the children. However, Aghini-Lombardi *et al* reported that in children aged 6–10 years in an area in Toscani, who had mild iodine deficiency (64 µg iodine/day), the reaction time was delayed compared with matched controls from an iodine sufficient area (142 µg iodine/day).<sup>27</sup> The cognitive abilities of the children were not affected.

A large series of investigations conducted in areas with moderate iodine deficiency have demonstrated the presence of definite abnormalities in the psychoneuromotor and intellectual development of children and adults who are clinically euthyroid and who do not exhibit the other signs and symptoms of endemic cretinism, that is, the most severe form of brain damage caused by iodine deficiency. The psychometric tests used to find evidence for these abnormalities are various and include locally adapted “culture free” intelligence tests. The findings include low visual-motor performances, motor skill, perceptual and neuromotor abilities, and low development quotients and intellectual quotients (IQ).<sup>11, 12, 20</sup>

Data collected in an area of moderate iodine deficiency in Sicily suggest that the impairment of intellectual development in these conditions represents the long term consequence of neonatal hypothyroidism<sup>28</sup>: systematic screening for congenital hypothyroidism performed on cord blood in this area showed that many neonates had severe biochemical hypothyroidism that was characterised by markedly raised serum TSH and low serum thyroxine. Thyroid function spontaneously reverted to normal at the time of control examinations which, due to local circumstances, occurred only at the age of 1–3 months. This pattern corresponds to a state of transient neonatal hypothyroidism. A small group of nine of these infants could be investigated again at the age of 6–10 years. At that time, their thyroid function was again normal but their global IQ and especially their performance IQ was significantly lower than in matched controls.<sup>29</sup>

This indicates that hypothyroidism occurring around birth, even if transient, can affect brain development and intellectual potential.

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 in “normal” children in such conditions 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.<sup>30–32</sup> More

globally, in their meta-analysis of 19 studies on neuromotor and cognitive functions in conditions of moderate to severe iodine deficiency, Bleichrodt and Born concluded that iodine deficiency results in a loss of 13.5 IQ points at the level of the global population.<sup>33</sup> The hindrance to the socioeconomic development of populations exposed to iodine deficiency that is due to brain damage and loss of intellectual potential is the reason why iodine deficiency and not only endemic goitre constitutes a major public health problem.

The most serious consequence of iodine deficiency on brain and physical development is endemic cretinism. 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 deaf mutism, squint, spastic diplegia, motor rigidity, shuffling gait, and of signs of severe thyroid insufficiency with dwarfism, myxoedema, and sexual immaturity. The prevalence of cretinism can be as high as 15% of the population. Because of geographical differences in the epidemiological, clinical, and biochemical features of those who have endemic cretinism around the world, the definition of the syndrome was not clear and resulted in considerable controversy until the aetiopathogenesis of the brain damage caused by iodine deficiency was better understood.<sup>34 35</sup>

#### **Aetiopathogenesis 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 and reported in this review paper have to be interpreted on the basis of two recent sets of findings.

##### (1) ROLES OF MATERNAL, FETAL, AND NEONATAL HYPOTHYROXINAEMIA

Mental retardation and endemic cretinism results from an insufficient supply of thyroid hormones to the developing brain. The physiological role of thyroid hormones can be defined so as to ensure the timed coordination of different developmental events through specific effects on the rate of cell differentiation and gene expression.<sup>2</sup> Thyroid hormone action is exerted through the binding of triiodothyronine to nuclear receptors, which regulate the expression of specific genes in different brain regions following a precise development schedule.<sup>2 3</sup> During the fetal and early postnatal life, triiodothyronine bound to nuclear receptors is entirely dependent on its local production from thyroxine via type II deiodinase.<sup>36</sup>

Thyroid function and regulation are autonomous in mother and fetus. Until recently, it has been considered that they are also independent because the transfer of thyroid hormones across the placenta, if any, is extremely limited.<sup>37</sup> In contrast, recent experimental and clinical data underline the importance of this transfer<sup>1 21 38 39</sup>: 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 for triiodothyronine are present in the fetus by 13 days' gestation and in the fetal brain by 14 days' gestation. The thyroxine and triiodothyronine available to early embryos and fetuses are of maternal origin. At term, 17.5% of fetal extrathyroidal thyroxine is still of maternal origin. These data extend the period of sensitivity of the brain to thyroid hormones well into the early phases of gestation when the supply of these hormones is entirely of maternal origin.

Similarly, in humans, thyroxine 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 triiodothyronine receptors and the amount of triiodothyronine 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.<sup>40</sup> At term, about 20% to 50% of cord serum thyroxine is still of maternal origin.

These data underline the importance of maternal thyroxinaemia 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 thyroxinaemia is normal and fetal serum thyroxine of maternal origin is able to protect fetal brain during the fetal life. This explains why, in sporadic congenital hypothyroidism, early and adequate substitutive therapy by thyroxine prevents almost entirely any brain damage in the affected children.<sup>41</sup>

In contrast, in severe iodine deficiency, maternal hypothyroidism does occur during pregnancy and the contribution of maternal thyroxine to the saturation of the triiodothyronine receptors of the brain of the growing fetus is decreased, resulting in the development of the neurological features of endemic cretinism.

##### (2) ADDITIONAL ROLES OF SELENIUM DEFICIENCY AND THIOCYANATE OVERLOAD

One stimulating new concept in the aetiology of brain damage, mental retardation, and endemic cretinism in severe iodine deficiency is the combined role of iodine and selenium deficiencies, together with thiocyanate overload resulting from a cassava based diet.<sup>35</sup>

Selenium is present in high concentrations in the normal thyroid. It is present in glutathione peroxidase and superoxide dismutase, the enzymes of the thyroid responsible for the detoxification of toxic derivatives of oxygen (hydrogen peroxide ( $H_2O_2$ ) and perhaps oxygen free radicals). It is also present in the type I iodothyronine 5'-deiodinase responsible for the peripheral conversion of thyroxine to triiodothyronine.<sup>22</sup>

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<sup>23</sup>: 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 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 thyroxine to triiodothyronine and thus increased availability of maternal thyroxine for the fetus and its brain.

This scheme explains why in situations characterised by isolated severe iodine deficiency such as New Guinea,<sup>16 17</sup> China, Indonesia,<sup>34</sup> and Thailand<sup>42</sup> the clinical picture of endemic cretinism is characterised by a dominant neurological picture and why, when selenium deficiency and thiocyanate overload are added, as in the DRC, the neurological signs are mitigated and the picture is dominated by severe hypothyroidism.<sup>35</sup>

The role of thiocyanate in the aetiology of endemic cretinism in Africa has been proposed because of the observation that people in areas with severe but uniform iodine deficiency exhibit cretinism only when a certain critical threshold in the dietary supply of thiocyanate is reached.<sup>43</sup> It has been shown experimentally in the rat that thiocyanate affects the development of the central nervous system during fetal life.<sup>44</sup> The action of thiocyanate is

entirely due to an aggravation of iodine deficiency resulting in fetal hypothyroidism.

Finally, all these abnormalities can be prevented when a normal iodine supply is provided to the mother before and during pregnancy and to the neonate and young infant during the critical period of brain development.<sup>35</sup>

In conclusion, it is now clearly demonstrated that the main impact of iodine deficiency on humans is much more on the brain than on the thyroid. Ongoing programmes of universal salt iodisation massively implemented around the world by Unicef and the WHO with the support of the ICCIDD, aim at the sustainable elimination of iodine deficiency as a cause of brain damage by and beyond the year 2000.

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