

# Selenium deficiency mitigates hypothyroxinemia in iodine-deficient subjects<sup>1-3</sup>

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**ABSTRACT** Studies were performed to assess the role of combined selenium and iodine deficiency in the etiology of endemic myxedematous cretinism in a population in Zaire. One effect of selenium deficiency may be to lower glutathione peroxidase activity in the thyroid gland, thus allowing hydrogen peroxide produced during thyroid hormone synthesis to be cytotoxic. In selenium-and-iodine-deficient humans, selenium supplementation may aggravate hypothyroidism by stimulating thyroxine metabolism by the selenoenzyme type I iodothyronine 5'-deiodinase. Selenium supplementation is thus not indicated without iodine or thyroid hormone supplementation in cases of combined selenium and iodine deficiencies. *Am J Clin Nutr Suppl* 1993;57:271S-5S.

**KEY WORDS** Iodine deficiency, selenium deficiency, myxedematous cretinism

## Introduction

Twenty-five years ago, radiolabeled selenomethionine was used as a marker of protein synthesis in the thyroid to help in the differential diagnosis of cold nodules (1). The interest in using selenium in thyroidology has declined with time as more specific and more sensitive clinical and technical diagnostic tests became available. However, since the demonstration that selenium intervenes in thyroid hormone metabolism in 1987, interest in selenium has been revived (2). Our purpose is to review the data concerning the role of selenium in the thyroid hormone metabolism of humans, taking advantage of the studies conducted in one of the most severely iodine-and-selenium-deficient populations in the world (3-5).

Northern Zaire has an endemic-goiter belt with 4 million people over a 2000-km<sup>2</sup> area. This endemic is characterized by a peculiarly elevated frequency of myxedematous cretinism, characterized by a clinical picture similar to that of sporadic cretinism—persistent hypothyroidism since early infancy resulting in dwarfism, infantile morphotype, and mental deficiency. This form of cretinism has to be differentiated from neurological cretinism, which is not systematically associated with persistent hypothyroidism or with stunted growth and which is characterized by profound neurological disorders (deaf-mutism, spastic diplegia, and extrapyramidal signs manifested by rigidity and dystonia of the proximal muscles in the limbs). In endemic areas other than Central Africa—Latin America, Asia, and New

Guinea—neurological cretinism is more common than is myxedematous cretinism (6).

This classical concept of two types of endemic cretinism, already described in 1908 (7), has recently been somewhat modified by the observation in China of a similar degree of neurological dysfunction in neurological cretins and in myxedematous cretins. Actually, in myxedematous cretins of Western China at least (8), an irreversible loss of thyroid function seems to be superimposed on the neurological impairment (9). Epidemiological and experimental data strongly support the hypothesis that neurological cretinism results from fetomaternal hypothyroidism during the end of the first trimester of pregnancy (10-12); during this period, the fetal gland is not yet working (fetal thyroid hormones are not synthesized before 10 wk of gestation), and the normal development of the central nervous system is critically dependent on an adequate placental transfer of thyroid hormones of maternal origin. According to the studies in China, fetomaternal hypothyroidism during the first trimester of pregnancy should involve neurological cretinism, whereas a persistent hypothyroidism during childhood should involve an involution of the thyroid gland, rendering the child definitely hypothyroid.

Contrasting with the observations in China, Central Africa has a high incidence of the "pure" form of myxedematous cretinism: in a very careful examination of 80 cretins in Ubangi, Zaire, 62 (78%) were myxedematous and 18 (22%) were clear examples of "pure" neurological cretinism (ie, without stunted growth or myxedema). Of the 62 cretins found to be myxedematous, 36 had no signs indicative of neurological cretinism; ie, they did not have deaf-mutism, spastic-dystonic motor disorders, or evidence of lower-motor-neuron-cell loss (13).

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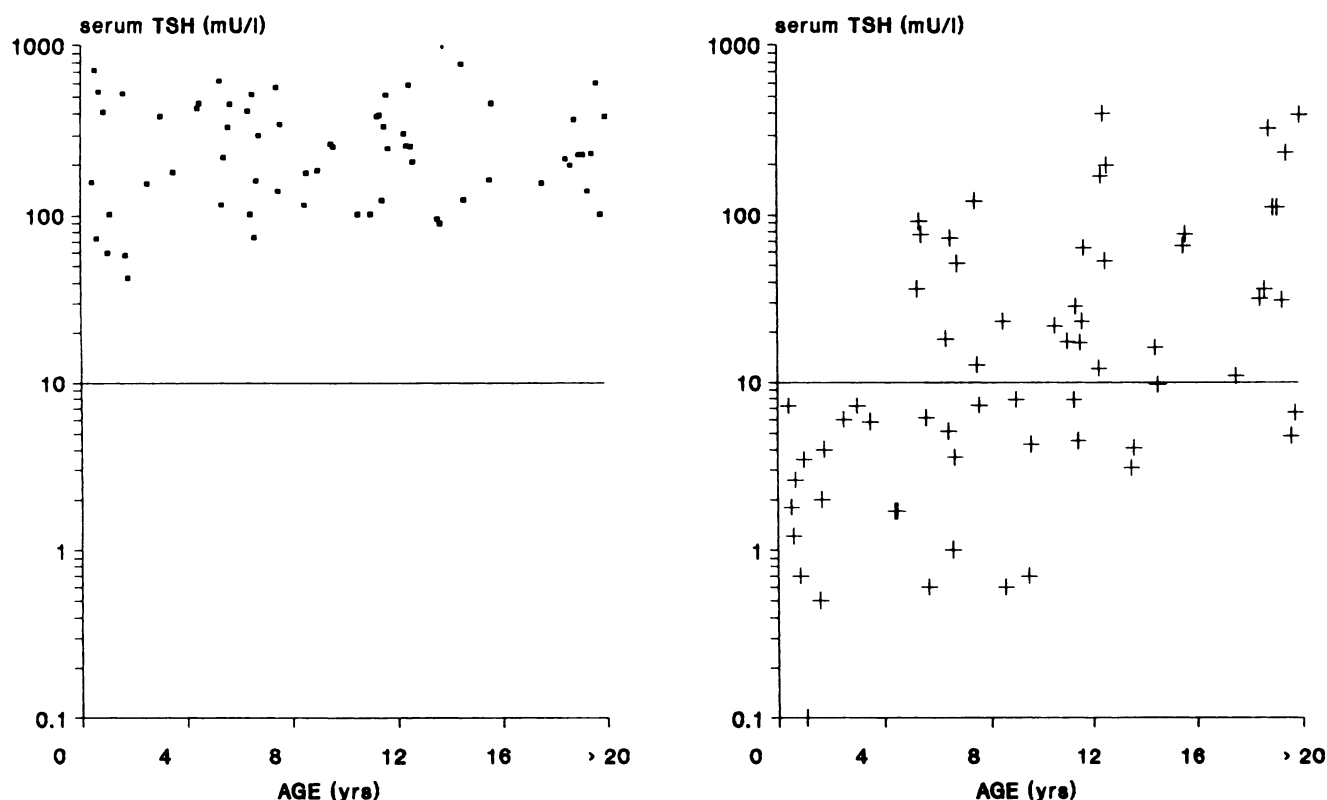


FIG 1. Distribution of the individual values of serum thyroid-stimulating hormone (TSH) before (left panel) and 5 mo after (right panel) iodine supplementation in cretins aged 0–42 y. The horizontal line is the upper limit of the normal reference range.

The epidemiological data suggest, then, that in Central Africa, but likely not in other iodine-deficient areas, that the developing fetus is less frequently exposed to hypothyroidism during a critical period at the end of the first trimester while the factors causing juvenile hypothyroidism and the evolution through myxedematous cretinism are present.

Recent investigations have been oriented toward the role of combined iodine and selenium deficiency in the etiology of endemic myxedematous cretinism in Zaire (14); the initial hypothesis was that iodine deficiency involves an increase in hydrogen peroxide ( $H_2O_2$ ) synthesis in the thyroid stimulated by thyroid-stimulating hormone (TSH) (15). An excess of  $H_2O_2$  in a thyroid gland depleted of one of the essential antioxidant mechanisms (selenium-glutathione peroxidase) could involve the progressive involution of thyroid function characteristic of myxedematous cretinism (16, 17).

To test this hypothesis, a selenium-supplementation trial was conducted in schoolchildren and in cretins of Ubangi, Zaire, in 1988, when the unique known function of selenium was that of being a cofactor of glutathione peroxidase. The time course of thyroid-function indexes was analyzed after selenium supplementation.

### Experimental studies

In the first part of this study, the data documenting the progressive loss of thyroid functional capacity with age in cretins are presented (16). In a second part, presented here, the effect

of selenium supplementation on the thyroid function of cretins and schoolchildren is presented.

#### *The responsiveness of the thyroid gland to iodine supplementation decreases with age in cretins*

Cretins aged 0–42 y were selected on clinical criteria and on biochemical criteria (TSH > 40 mU/L and thyroxine ( $T_4$ ) < 64 nmol/L) in rural villages of Ubangi, and iodized oil (0.5 mL Lipiodol IM; Guerbet, Aulnay-sous-Bois, France) was administered. **Figure 1** shows the distribution of the individual TSH values before and 5 mo after iodine supplementation. Before treatment, the individual serum TSH values were homogeneously distributed according to age, with a mean serum TSH concentration (geometric mean  $\pm$  1 SD) of 220.1 mU/L (range 105.6–458.9 mU/L) ( $n$  = 64). Five months after treatment, serum TSH was < 10 mU/mL in the 14 cretins < 4 y old, but in older cretins, an increasing proportion of subjects with age kept elevated serum TSH values; the mean serum TSH concentrations after treatment increased progressively with age: aged 0–4 y, 1.8 mU/L (0.5–6.4 mU/L) ( $n$  = 14); aged 5–15 y, 13.0 mU/L (2.4–71.7 mU/L) ( $n$  = 36) ( $P$  < 0.001 vs 0–4 y); aged 15–42 y, 40.6 mU/L (9.6–170.6 mU/L) ( $n$  = 14) ( $P$  < 0.001 vs 5–15 y). **Figure 2** shows the distribution of the individual values of serum  $T_4$  before and 5 mo after iodine supplementation. Before treatment, the individual serum  $T_4$  values were homogeneously distributed according to age, with a mean serum  $T_4$  concentration (arithmetic mean  $\pm$  1 SD) of 19.3  $\pm$  17.1 nmol/L ( $n$  = 65). Five months after treatment, serum  $T_4$  was > 77



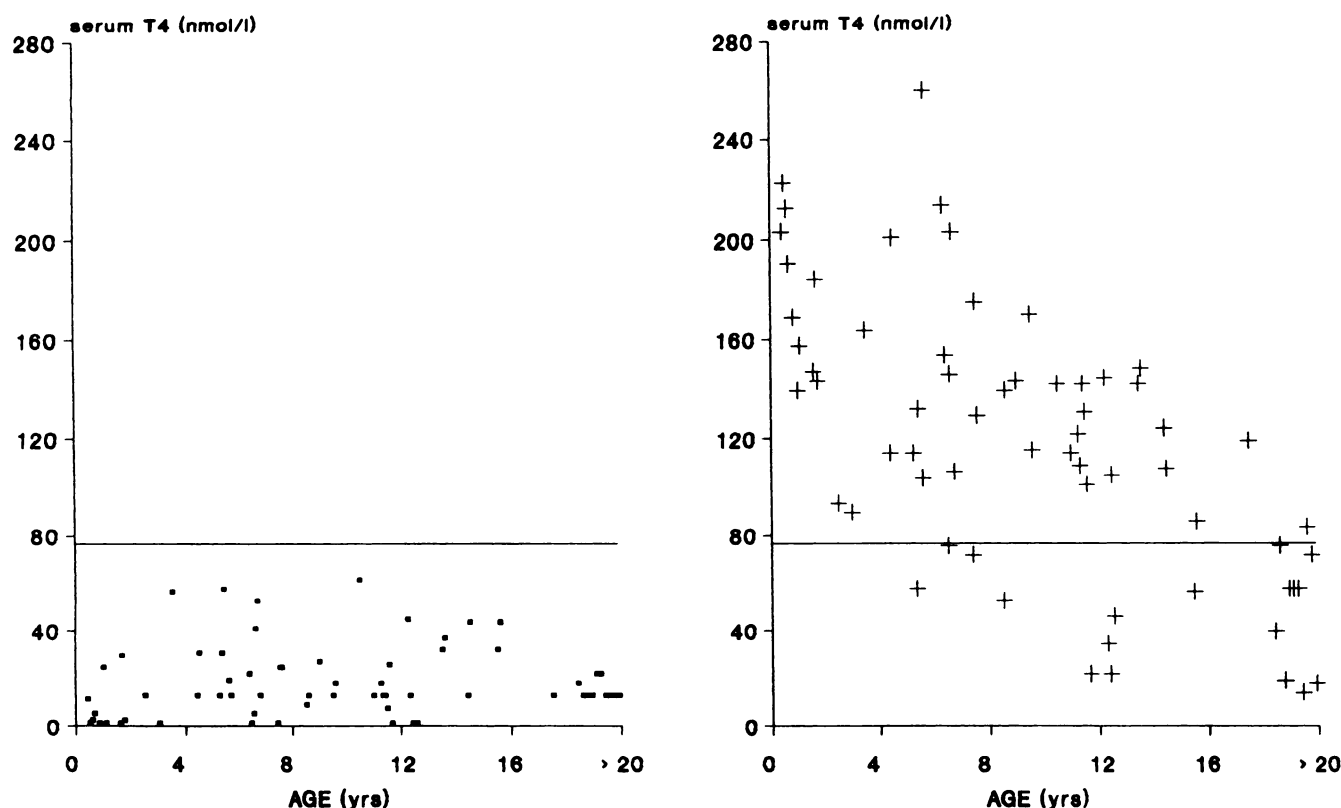


FIG 2. Distribution of the individual values of serum thyroxine ( $T_4$ ) before (left panel) and 5 mo after (right panel) iodine supplementation in cretins aged 0–42 y. The horizontal line is the upper limit of the normal reference range.

nmol/L in the 15 cretins < 4 y old, but in older cretins, an increasing proportion of subjects remained hypothyroxinemic; the mean serum  $T_4$  concentrations after treatment decreased progressively with age: 0–4 y,  $162.9 \pm 41.2$  nmol/L ( $n = 13$ ); 5–15 y,  $119.2 \pm 55.8$  nmol/L ( $n = 37$ ) ( $P < 0.001$  vs 0–4 y); 15–42 y,  $66.4 \pm 36.0$  nmol/L ( $n = 14$ ) ( $P < 0.001$  vs 5–15 y).

#### *Selenium supplementation in iodine-and-selenium-deficient subjects aggravates hypothyroxinemia*

Schoolchildren and cretins of villages surrounding Karawa were supplemented for 2 mo with a physiological dose of selenium ( $50 \mu\text{g Se/d}$  as selenomethionine per os) in the absence of iodine supplementation. Serum selenium was very low at entry into the study and was similar in schoolchildren and in cretins [ $\bar{x} \pm 1$  SD: schoolchildren,  $343 \pm 190$  nmol/L ( $n = 23$ ); cretins,  $296 \pm 116$  nmol/L ( $n = 9$ )]. Selenium was in the normal range (60–250 nmol/L) in all subjects after 2 mo of selenium supplementation, with a mean serum concentration of  $944 \pm 285$  nmol/L in the 23 schoolchildren and of  $1725 \pm 547$  nmol/L in the 9 cretins. Erythrocyte glutathione peroxidase activity was very low at entry into the study, with lower activity in cretins than in schoolchildren [schoolchildren,  $2.97 \pm 1.84$  U/g Hb ( $n = 24$ ); cretins,  $1.42 \pm 1.71$  U/g Hb ( $n = 9$ ) ( $P < 0.05$ ); after 2 mo of selenium supplementation, mean erythrocyte glutathione peroxidase activity increased significantly in both groups without reaching the normal reference range in schoolchildren ( $9$ – $16$  U/g Hb) [schoolchildren,  $5.76 \pm 2.19$  U/g Hb ( $n = 23$ ) ( $P < 0.01$  vs entry into the study); cretins,  $10.33 \pm 5.31$  U/g Hb ( $n = 9$ ) ( $P < 0.001$  vs entry in the study)].

Figure 3 shows individual values and the mean concentrations of serum  $T_4$  before and 2 mo after selenium supplementation in schoolchildren and in cretins. In schoolchildren, at entry into the study, the individual values of serum  $T_4$  were distributed in the normal (9 cases, 39%) and in the hypothyroxinemic range (14 cases, 61%); 2 mo after selenium supplementation, all individual values of serum  $T_4$  initially in the normal range ( $> 77$  nmol/L) decreased, and only three cases of the nine initially euthyroxinemic schoolchildren kept a serum  $T_4$  in the normal range; mean serum  $T_4$  concentration in schoolchildren decreased from  $72.74 \pm 45.21$  nmol/L to  $47.97 \pm 23.59$  nmol/L ( $n = 23$ ) ( $P < 0.001$ ). In cretins, at entry into the study, all nine individual values of serum  $T_4$  were severely decreased ( $< 30$  nmol/L); 2 mo after selenium supplementation, all eight detectable ( $> 1.3$  nmol/L) serum  $T_4$  values decreased further, whereas the unique serum  $T_4$  value initially at the limit of detection remained at that level 2 mo later; mean serum  $T_4$  decreased from  $12.8 \pm 5.1$  nmol/L to  $2.5 \pm 2.5$  nmol/L ( $n = 9$ ) ( $P < 0.001$ ).

The other thyroid-function indexes in schoolchildren and in cretins evolved as follows (4, 5). In schoolchildren, the serum free thyroxine ( $FT_4$ ) index decreased from  $11.8 \pm 6.7$  nmol/L to  $8.4 \pm 4.1$  nmol/L ( $n = 23$ ) ( $P < 0.01$ ), and serum reverse triiodothyronine ( $rT_3$ ) decreased from  $12.4 \pm 11.5$  nmol/L to  $9.0 \pm 7.2$  nmol/L ( $n = 23$ ) ( $P < 0.05$ ); mean serum  $T_3$  and mean serum TSH remained stable during the selenium-supplementation trial. In cretins, the serum  $FT_4$  index remained the same or decreased to an undetectable level in all nine cretins; mean serum  $T_3$  concentration decreased from  $0.98 \pm 0.72$  nmol/L to  $0.72 \pm 0.29$  nmol/L ( $n = 9$ ) ( $P = \text{NS}$ ), and the two cases of

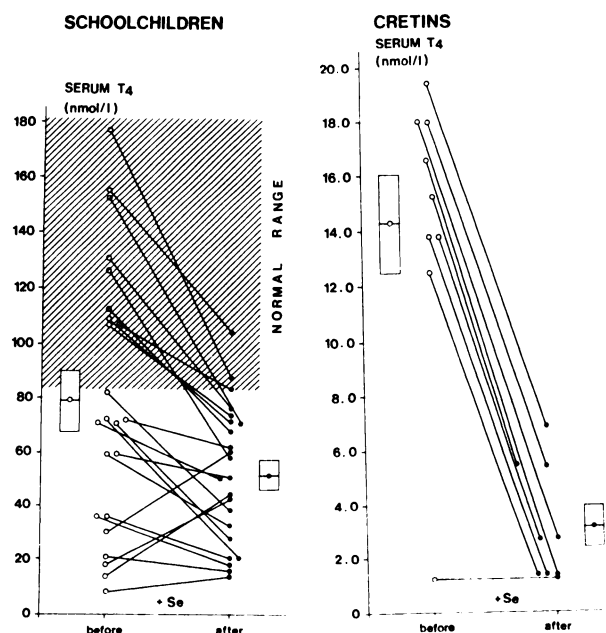


FIG 3. Mean concentrations and individual values of serum T<sub>4</sub> before and 2 mo after selenium supplementation (50  $\mu$ g selenium/d as selenomethionine tablets) in schoolchildren aged 9–15 y (left panel) and in cretins aged 8–25 y (right panel). The normal reference range of serum T<sub>4</sub> is indicated by the hatched area in the left panel. Note that the serum T<sub>4</sub> scale is 10 times lower in the right panel than in the left panel.

cretins who were initially in a normal range of serum T<sub>3</sub> (1.32–2.90 nmol/L) presented T<sub>3</sub> values outside the lower limit of normal after selenium supplementation. Serum rT<sub>3</sub> was initially at the undetectable level in the nine cretins (3.0 pmol/L), and it remained so 2 mo after selenium supplementation. Mean serum TSH increased significantly from 262 mU/L (218–316 mU/L) to 363 mU/L (304–432 mU/L) ( $n = 9$ ) ( $P < 0.001$ ).

## Discussion

Persistent hypothyroidism since early life in cretins of northern Zaire is associated with a progressive loss of thyroid functional capacity. This degenerative process is mainly postnatal, and it is not until 5 y of age that the thyroid becomes incapable of restoring a euthyroid state after iodine supplementation.

The frequency of this “pure” form of myxedematous cretinism is peculiarly elevated in Central Africa, whereas in other endemic areas, myxedematous features seem to be superimposed on neurological cretinism, resulting in a clinical picture of “mixed” cretinism (neurological cretinism combined with myxedematous features) (8).

This clinical epidemiological observation has not been contradicted by various independent observers (6, 13, 16) who have worked in the field, and it raises two questions: 1) Why should myxedematous cretinism be more frequent in Central Africa than in other endemic areas? 2) Why should myxedematous cretins be protected from neurological disorders in Central Africa and not in other endemic areas?

The observation of a severe selenium deficiency combined with iodine deficiency offers an attractive unifying hypothesis to answer both questions (Figure 4). Concerning the hypothesis

that selenium plays a role in the pathogenesis of myxedematous cretinism, it is proposed that selenium deficiency involves a lack of glutathione peroxidase activity in the thyroid, and the synthesis of H<sub>2</sub>O<sub>2</sub> in excess due to thyrotropin stimulation induces cytotoxicity. Figure 4 shows also that selenium is the cofactor of iodothyronine 5'-deiodinase, as recently proven (18, 19). This is likely the mechanism by which serum T<sub>4</sub> and serum reverse T<sub>3</sub> decrease after selenium supplementation in iodine-and-selenium-deficient subjects. Schoolchildren and cretins differ in the remaining functional capacity of the gland: in schoolchildren after selenium supplementation, the lowering of serum T<sub>4</sub> is not accompanied by a decrease in serum T<sub>3</sub>; it is not evident, then, that the aggravation of hypothyroxinemia means an aggravation of hypothyroidism, at least for a few months; a better intracellular conversion of T<sub>4</sub> to T<sub>3</sub> could even mitigate hypothyroidism, as the decrease in serum TSH after selenium supplementation in initially hypothyroxinemic children suggests (20). By contrast, in cretins, the depleted thyroid gland is unable to adapt to the increased metabolism of serum T<sub>4</sub>, and the aggravation of hypothyroxinemia is clearly associated with an aggravation of hypothyroidism.

Considering the relatively low frequency of neurological cretinism in Northern Zaire, it is proposed that selenium deficiency mitigates maternal hypothyroxinemia during the critical phase, when the development of the fetal central nervous system is

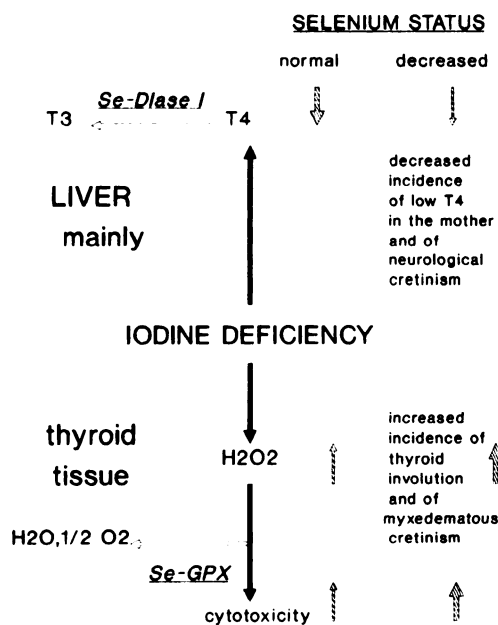



FIG 4. Proposed model of interaction of selenium deficiency with cretinism. Selenium is the cofactor of two enzymes, glutathione peroxidase (Se-GPX) and type I 5'-deiodinase (Se-DIase I). A lack of Se-GPX in the thyroid could involve a decrease of the defense mechanisms against hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and an increased cytotoxicity, resulting in an involution of the thyroid functional capacity characteristic of endemic myxedematous cretinism. On the other hand, a lack of Se-DIase I could involve a decrease in the conversion of serum T<sub>4</sub> into T<sub>3</sub>, mainly in the liver, and, in pregnant women, could increase the availability of T<sub>4</sub> of maternal origin for the fetus during the critical period of brain development when the pool of thyroid hormones in the fetus is entirely dependent on an adequate supply of maternal thyroid hormones by placental transfer (before the 10th wk of gestation).

closely dependent on an adequate supply of thyroid hormones of maternal origin. Moreover, selenium deficiency in the fetus could diminish the utilization of  $T_4$  in the peripheral tissues, and keep it preferentially for the central nervous system (CNS); in the case that type II 5'-deiodinase, which converts  $T_4$  to  $T_3$  in the CNS, is not a selenoenzyme, this would favor fetal CNS.

Despite the speculative nature of this proposed model, it is clear that selenium supplementation should not be undertaken without concomitant iodine supplementation in an iodine-and-selenium-deficient population. 

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