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Understanding Prenatal Iodine Deficiency

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1. Introduction

Iodine deficiency is a worldwide Public Health problem, mainly in pregnant women and infants, which causes permanent and irreversible sequels in the Central Nervous System (CNS) of the progeny when daily iodine intake does not reach optimal levels. Pharmacological iodine supplements have been recommended during pregnancy and lactation periods in regions with low iodine intake diet.

In recent years, maternal hypothyroxinemia has been recognized as the biochemical condition responsible for the alterations in the processes of neural development in the embryo and fetus associated to iodine deficiency.

Research Methods: The objective of this study was to review the available scientific evidence on the crucial role of iodine in early stages of neural development, to understand the international scheduling recommendations about an adequate iodine intake in vulnerable populations groups.

Iodine is a micronutrient essential for the synthesis of thyroid hormones¹. The thyroid gland takes iodine from the diet, stores it and subsequently incorporates it into other molecules, to produce two types of thyroid hormones as a final product: triiodothyronine (T3) and thyroxine (T4) containing three and four iodine atoms respectively. Both circulate in blood bound to proteins and act on specific receptors. The free T3 is metabolically more active, but the T4 is, as we shall see, indispensable at specific developmental stages.

The thyroid hormones are involved in many metabolic and developmental processes, and they exert a broad range of actions on every tissue of the body: body temperature regulation, somatic growth. Further, it is essential for the proper development and function of the Central Nervous System.²

Since the first epidemiological studies conducted by Pharoah³ and Thilly⁴ in the 70's, the association between iodine deficiency in pregnant women and fetal neurological damage has been extensively reviewed and proven in scientific literature. In fact, the need to provide iodine supplementation to pregnant women in iodine-deficient regions is considered as proven by scientific evidence.⁵

Many of these studies are focused on regions where severe iodine deficiency is endemic and coexisting with mixedematous cretinism.⁶ The understanding of the neurological effects of hypothyroidism on infants was partially obtained from mothers with clinically overt hypothyroidism.^{7,8} All these factors have contributed to a general awareness that iodine deficiency is a problem restricted to specific geographic areas and to well-defined at-risk populations (hypothyroidism, goiter and malnutrition)⁹

For a long time, there has been a prevailing belief that the main factor responsible for alterations in fetal neurological development was maternal hypothyroidism (defined as elevated serum TSH levels) in the early stages of pregnancy.^{8,10} Thus, when a pregnant woman was found to have normal thyroid function, neurodevelopmental alterations in the fetus were systematically discarded.¹¹

Along history, some contradictions have arisen from mixing different concepts as endemic cretinism, congenital hypothyroidism, iodine deficiency, etc¹². Fortunately, such contradictions have been clarified by the advances in our understanding of thyroid physiology during pregnancy^{13,14}, the transfer of maternal thyroid hormones to the fetus^{15,16} and the increasingly complete characterization of thyroid hormone receptors in placental and embryo tissues.¹⁷ Nevertheless, only the most recent studies have given satisfactory explanation of the possible role of thyroid hormones (maternal and fetal) during critical stages of fetal neurological development.¹⁸ Basing on these recent works, the relevance of an adequate balance of iodine during the early stages of life is considered proven.

2. Iodine deficiency and pregnancy

Pregnancy is accompanied by dramatic changes in the thyroid function, which are the result of a complex combination of factors specific to pregnancy that altogether stimulate the maternal thyroid machinery.¹⁴

During the first half of gestation the maternal thyroid undergoes some changes:

- Progressive increase of thyroglobulin, which reduces free fraction of thyroxine.
- The human chorionic gonadotropin has TSH-like effect and acts by directly stimulating the maternal thyroid.
- Meanwhile, the fetal thyroid is kept inactive and will not be functioning until 20 weeks of gestation.
- The only source of thyroid hormones in the fetus throughout the first half of pregnancy is thyroxine of maternal origin.

In healthy pregnant women with adequate iodine levels, pregnancy mainly involves a higher demand of thyroid hormones. The thyroid gland regulates the release of hormones to achieve a new balance, and maintains this balance until the end of the gestation process¹⁹. In general, the higher hormone need can only be met by a proportional increase in hormone release, which directly depends on the intake of iodine through the diet. At present, we know that iodine nutritional needs increase in all pregnant women due both to the higher hormone need and to the higher glomerular filtration rate²⁰. This adaptation is achieved without difficulty by the thyroid machinery²¹.

Conversely, when the thyroid gland fails –due, for example, to iodine deficiency–, such changes in thyroid parameters may not be adequately compensated and adaptation mechanisms fail^{13, 21}

Obviously, the more severe iodine deficiency, the more serious fetal and maternal consequences are. However, it has been shown that such alterations can be found when pregnancy occurs in healthy women residing in moderately iodine-deficient areas²².

3. Thyroid hormones and fetal brain development

3.1 Background

In 1888, the Clinical Society of London prepared a report which emphasized the key role of the thyroid gland for normal brain development²³. The members of this committee reached this conclusion after observing that patients with both endemic and sporadic cretinism showed clear evidence of mental retardation.²⁴

Initially, endemic cretinism was thought to be a congenital disease^{25, 26}. However, the prenatal origin of this syndrome was confirmed when a clinical trial with iodized oil showed that it could be successfully prevented exclusively when iodine was supplied to the mother before conception.³

The classic works by Pharoah et al.^{3,27} in Papua New Guinea in the 70's, and later by Thilly et al⁴ in Ubangi (Zaire) and Malawi, provided a thorough description of the clinical symptoms of endemic cretinism (in its myxedema and neurological forms), which were characteristic of regions with severe endemic goiter.

These early studies supported the idea that severe iodine deficiency in the mother produces irreversible neurological damage in the fetus during critical development stages¹². Cases of intrauterine deaths, miscarriages, death in childhood and the birth of cretins to women with biochemical evidence of iodine deficiency (very low free T4 levels) without clinical signs of hypothyroidism were described.^{28, 29}

In 1976, Pharoah et al²⁷ pointed out that iodine deficiency was different from untreated myxedema and from congenital hypothyroidism, which are usually associated with menstrual disorders, infertility or repeated miscarriage.

Later, studies on iodine deficiency and its effects at the reproductive age and on progeny almost fell into oblivion in the scientific scene. It was believed that iodine deficiency had an impact only in certain geographic areas with severe endemic goiter, and that such dramatic consequences had been eradicated both in Europe and in the United States.³⁰

Thus, a misconception of the pathophysiology of neurological deficit caused by iodine deficiency was established. The placenta was thought to prevent the transfer of thyroid hormones.³¹ According to this theory, the fetal brain would develop in the absence of maternal transfer of these hormones³² and, therefore, neurological damage could be prevented by hormone supplementation therapy at birth.¹³

In the following years in Europe, further clinical experience emphasized the significance of getting the diagnosis of congenital hypothyroidism, and initiating appropriate supplementation therapy as soon as possible after birth. The development of increasingly more precise^{33, 34} screening tests of thyroid function allowed to identify congenital hypothyroidism at birth and begin treatment without delay³⁵.

However, clinical reports in regions with severe iodine deficiency suggested a different reality: there was a clear correlation between maternal hypothyroxinemia levels and the severity of neurological damage in the progeny. The lower the maternal FT4, the more serious the effects on the fetus, causing irreversible neurological and mental abnormalities at birth that could only be prevented by treating maternal hypothyroxinemia throughout the first half of gestation.³⁶ Subsequent interventions could not prevent all disorders.

But it was not until 1999 –when Haddow et al.³⁷ published their classic article in the *New England Journal of Medicine*– that iodine deficiency in pregnant women in developed countries was seen again as a problem also affecting populations that were so far thought to be safe from this endemic disease. Haddow et al.³⁷ found that infants of women with undiagnosed hypothyroidism (TSH above the 98th percentile) during pregnancy had lower scores on tests related to intelligence, attention, language, reading skills, school and visual-motor performance, and that such differences with the other infants were statistically significant in the 15 tests performed.

That same year, Pop et al.³⁸ published an article proving that fetal neural development is not only affected when the mother has subclinical hypothyroidism, but it is just enough that

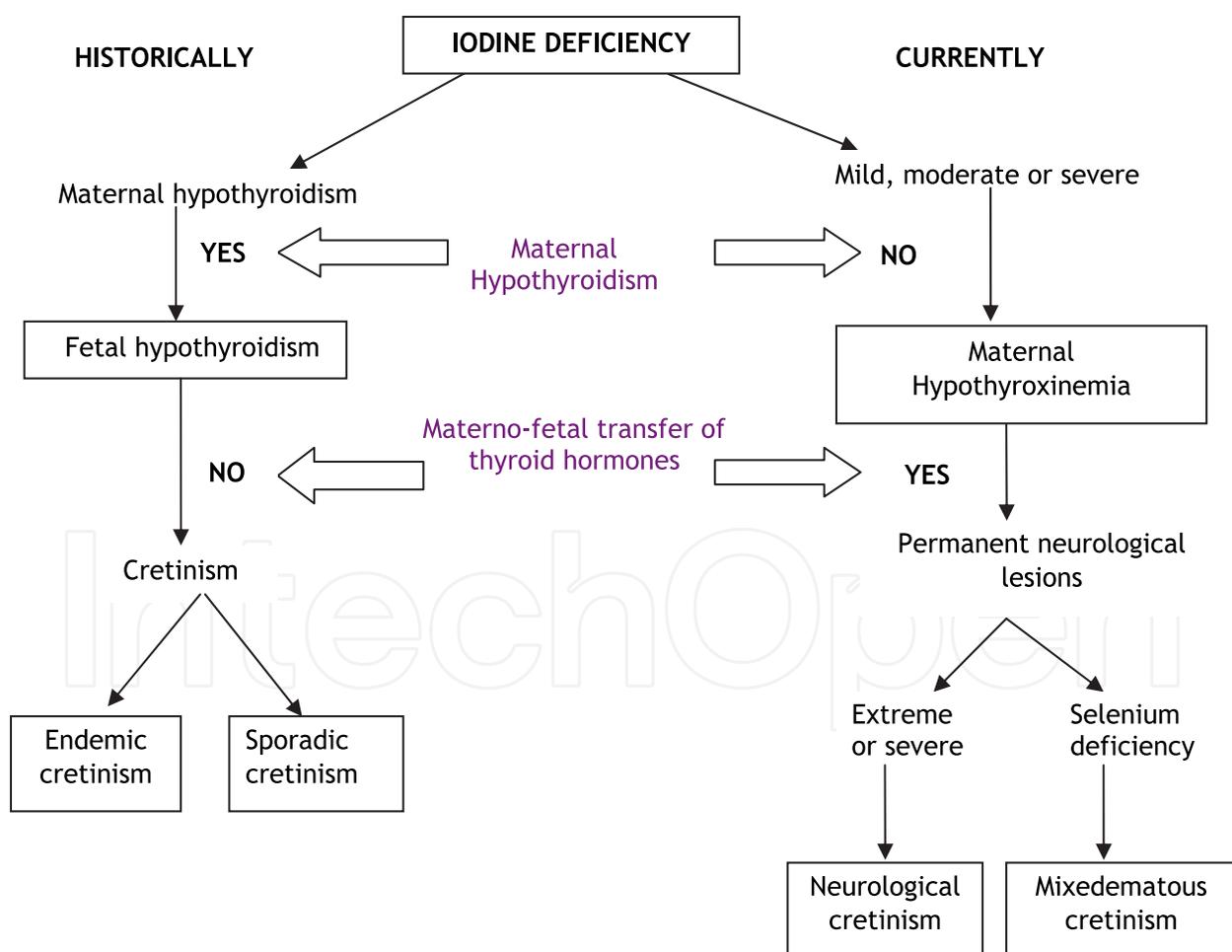


Fig. 1. Fetal and neonatal effects of iodine deficiency during pregnancy. The main advance is that maternal hormone transfer to the fetus during pregnancy has been definitely accepted, as well as the existence of damage in the progeny in absence of maternal hypothyroidism.

there is a previous stage of "maternal hypothyroxinemia" in the early stages of pregnancy. In their article, the authors showed that infants of mothers with T4 levels below the 10th percentile at the 12th week of gestation had significantly lower scores on the Bayley Psychomotor Development Scale at 10 months of age, compared with infants of mothers with higher free T4 levels.

In 2000, Morreale de Escobar et al.³⁶ presented epidemiological and experimental evidence strongly suggesting that first-trimester hypothyroxinemia (a low for gestational age circulating maternal free T4, whether or not TSH is increased) produces an increased risk for poor neuropsychological development of the fetus. The damage would be caused by decreased availability of maternal T4 to the developing brain.

Further, poor brain development occurs both in regions with severe iodine deficiency, and in regions with slight or moderate deficiency.^{22, 28}

The identification of hypothyroxinemia as a factor which causes neurological damage in progeny –regardless whether or not the mother has hypothyroidism– is a landmark for the study of iodine deficiency in Europe.^{32,36}

Figure 1 shows the differences between the classic and current understanding of the physiopathology of iodine deficiency.

4. Thyroid hormones and fetal neurological development

In humans, cerebral cortical development occurs between the 6th and the 24th week of gestation. The cortical plate begins to form around day 54 (8 weeks of gestation). Cortical neuronal migration mostly occurs between the week 8th and 24th (before the end of the second trimester), and generally before the onset of fetal thyroid hormone secretion occurs in the middle of gestation³⁹.

From a didactical perspective, fetal neurological development takes place in three stages relying on the thyroid hormone⁴⁰ (Figure 2):

1. The first stage takes place before the fetus starts producing thyroid hormones, and ends between the week 16th and 20th of gestation. During this period, thyroid hormone exposure comes only from maternally synthesized hormones, which influence neuronal proliferation and migration of neurons into the neocortex and hippocampus.
2. The second stage occurs during the remainder of pregnancy after the onset of the fetal thyroid function, when the developing brain derives its supply of thyroid hormones from both the fetus and the mother. At this moment, thyroid hormones will trigger neurogenesis, neuronal migration, axonal outgrowth, dendritic branching and synaptogenesis, and the onset of glial cell differentiation and migration, and myelination.
3. The third stage takes place during the neonatal and post-natal period when thyroid hormone supplies to the brain are entirely derived from the child and critical for continuing maturation. At this stage, thyroid hormones affect granule cell migration in the hippocampus and cerebellum, including the migration of cerebellar Purkinje cells. Gliogenesis and myelination continue during this stage.

Thyroid hormone receptors (TR alpha and beta) bind T3 with very high affinity, and act as ligand-induced transcription factors modulating the expression of different T3-dependent

target genes¹⁸. Thus, although circulating levels of T4L are 4-fold higher than those of T3L, the thyroid hormone receptor has at least 15-fold more affinity for T3⁴⁰, which indicates that T4 is a prohormone that must be converted into T3 before the onset of thyroid hormone function.

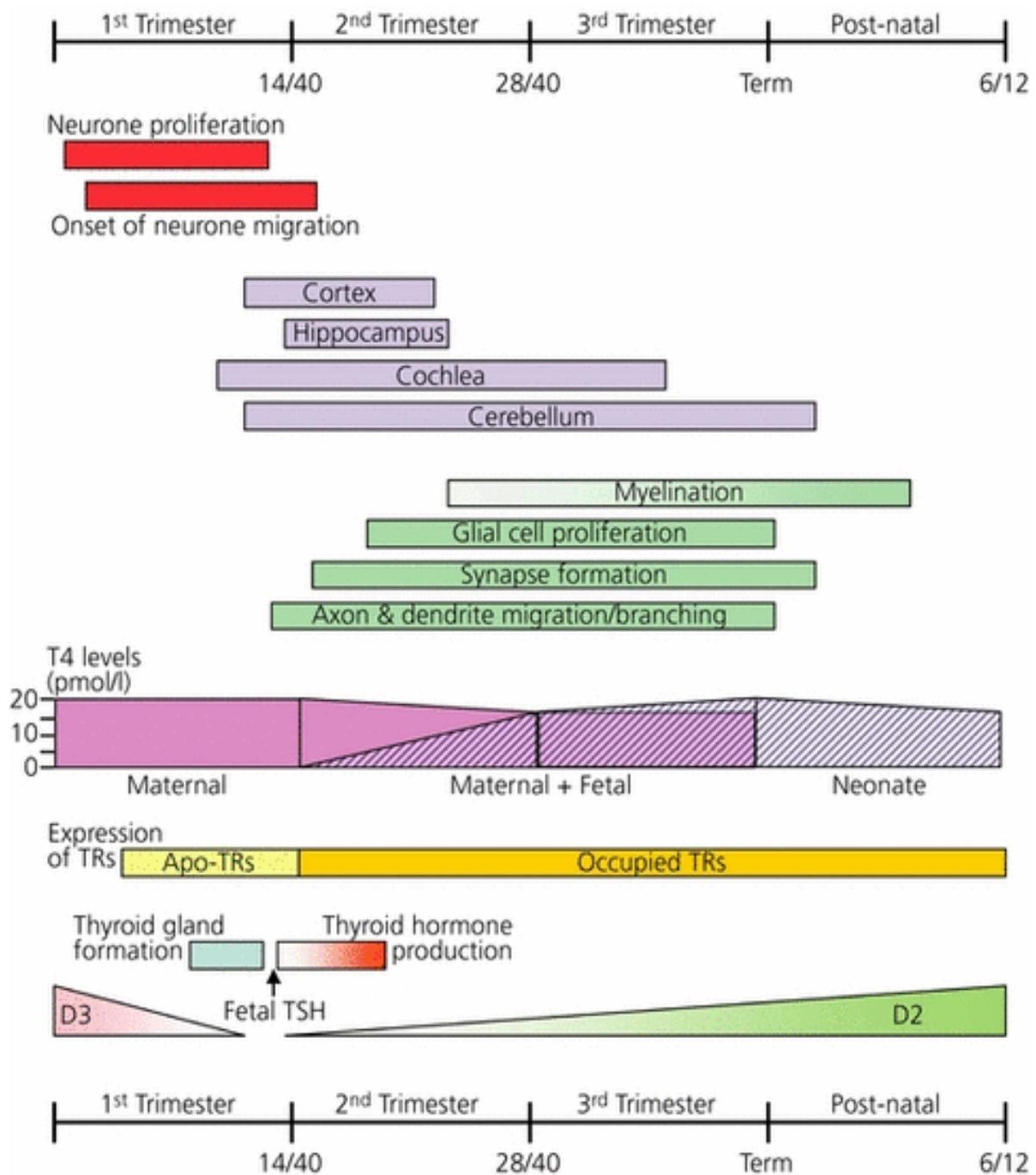


Fig. 2. Relationship between thyroid hormone action and brain development. In the first trimester of gestation, early neuronal proliferation and migration is dependent on maternal thyroxine (T4). In fetal tissues, deiodinase (ID-III, D3) enzyme expression falls and marks the onset of the fetal thyroid development. (D2: deiodinase ID-II). TRs: thyroid hormone receptors. From Williams GR. *Neurodevelopmental and Neurophysiological Actions of thyroid hormones*. *J Neuroendocrinol* 2008; 20: 784-794.

TR alpha and beta receptors express in most tissues, but their distribution varies from one tissue to another, which constitutes a control mechanism of T3 action that is specific in time and space.^{41,42}

Towards the end of the first trimester, development of the hypothalamic-pituitary axis has occurred and causes an increase in TSH secretion that marks the onset of fetal thyroid hormone production. Then starts the activating deiodinase enzyme ID-II expression and increases the occupation of thyroid hormone receptors by T3.

Continuing development of the brain in the second and third trimesters relies increasingly on the T4 produced by both the fetus and mother. Continued post-natal development is entirely dependent on neonatal thyroid hormone secretion.

Thyroid hormones intervene directly or indirectly in most of the neurodevelopmental processes of the embryo and the fetus. This would explain that thyroid deficiency in early pregnancy causes irreversible effects^{43,44}.

Thyroid hormone receptors have been proven to express profusely both in neurons and in glial cells (astrocytes and oligodendrocytes)^{45,46}.

At neuronal level, thyroid hormones would act as “cofactors”, favoring the expression of certain patterns of genes involved in axonal and dendrite outgrowth, and in the formation of synapses, myelination, cell migrations, and proliferation of specific cell populations³⁹.

For a proper neuronal function (synaptic transmission, laminar cytoarchitecture of the cerebral cortex) appropriate interaction with glial cells is required⁴⁷. In this sense, thyroid hormones favor proliferation of oligodendrocyte precursor cells and their differentiation into mature oligodendrocytes (which make the myeline sheath)⁴⁶.

At the same time, thyroid hormones are involved in the maturation of radial glial cells, which are directly involved in neuronal migration into the different layers of the cerebral cortex.⁴⁸ Finally, thyroid hormones are directly involved in the development and maturation of glial cells in specific brain areas, as the hippocampus or the cerebellum.⁴⁴

Thorough this sequence of events, it should be considered:

- That fetal neurodevelopment follows a very precise and limited sequence of events⁴⁷. The response period of the cell is what is called competence. The same cell will not respond before or after this period.
- That the maturation sequence is not formed by a succession of independent events, but rather by cascading events where each anomaly.^{49,50}

5. Thyroid hormone transfer and maternal hypothyroxinemia

In humans, maternal thyroid hormones are transferred to the fetus and the embryo during pregnancy. In fact, during the first half of gestation, the mother is the sole source of thyroid hormones^{51,52}.

Under normal conditions, embryonic tissues have a set of security mechanisms protecting their development. Some of these mechanisms are physical barriers (placenta and extraembryonic membranes) that avoid free transfer of maternal thyroid hormones into the fetus, and expose it to the same plasma fluctuations that occur in maternal blood serum^{53,54}.

Another security mechanism is the presence of deiodinase enzymes in fetal cerebral tissues^{55,56}. Deiodinase enzymes take maternal free thyroxine (T4L) and subsequently convert it into T3, but do not allow direct transfer of maternal T3⁵⁷. FNAs were made to obtain samples of fetal serum, and T4 concentrations in fetal serum were found to rely directly on maternal thyroxinemia⁵⁸.

In case of nutritional iodine deficiency, the organism activates self-regulating mechanisms where T3 is synthesized prevailing over T4, as a way to save iodine¹⁵ (Figure 3). This leads to a situation of maternal hypothyroxinemia, which is the fall of T4L levels in plasma, but presenting normal circulating T3L and TSH levels^{36,57}.

Maternal hypothyroxinemia is defined as:

- A “biochemical” status (low T4L levels with normal TSH values).
- It appears in healthy pregnant women (without any clinical sign or underlying thyroid pathology).
- It reflects a deficient nutritional status where the daily dietary intake of iodine is not adequate to meet iodine needs during pregnancy.
- It indicates maternal inability to guarantee adequate T4 transfer to the embryo, which is required for proper neurological development^{36,38}.

At present there is solid evidence that maternal hypothyroxinemia (low T4L) during the first half of gestation is the main cause of neurological alterations in the embryo and the fetus^{57,59}. Such alterations are permanent and irreversible.

All levels of iodine deficiency (low, moderate or severe) affect the maternal and neonatal thyroid function, and infant’s mental development²².

6. Hypothyroxinemia and neurodevelopment

Animal models for iodine deficiency during pregnancy on development of the CNS have been developed for monkeys, sheep and rats.² These studies have shown changes in cerebellum with reductions in weight and cell number, and delayed maturation. The influence of maternal hypothyroxinemia on neocortical development has been recently studied in rats and mice.⁶⁰

6.1 Altered migration during corticogenesis

The cerebral cortex is composed of neuronal layers with specific functions.³⁹ To form this cytoarchitecture, neurons undergo a Tangential migration from the basal epithelium into the upper layers of the cortex⁴⁴. Neuronal migration is highest between the 11th and the 14th week of gestation, coinciding with the T4 peak in maternal blood serum during gestation.³²

During this migration, neurons use glial cells like the steps of a stairway to climb into the upper layers^{39,47}. This interaction between glial cells and neurons is enabled by thyroid hormones.^{50,60}

Studies on radial migration during corticogenesis have revealed that in cerebral cortex of hypothyroid rats, the radial positioning of migrating neurons is altered^{48,49}, resulting in abnormally located Heterotopic neurons in the subcortical white matter (Figure 3)².

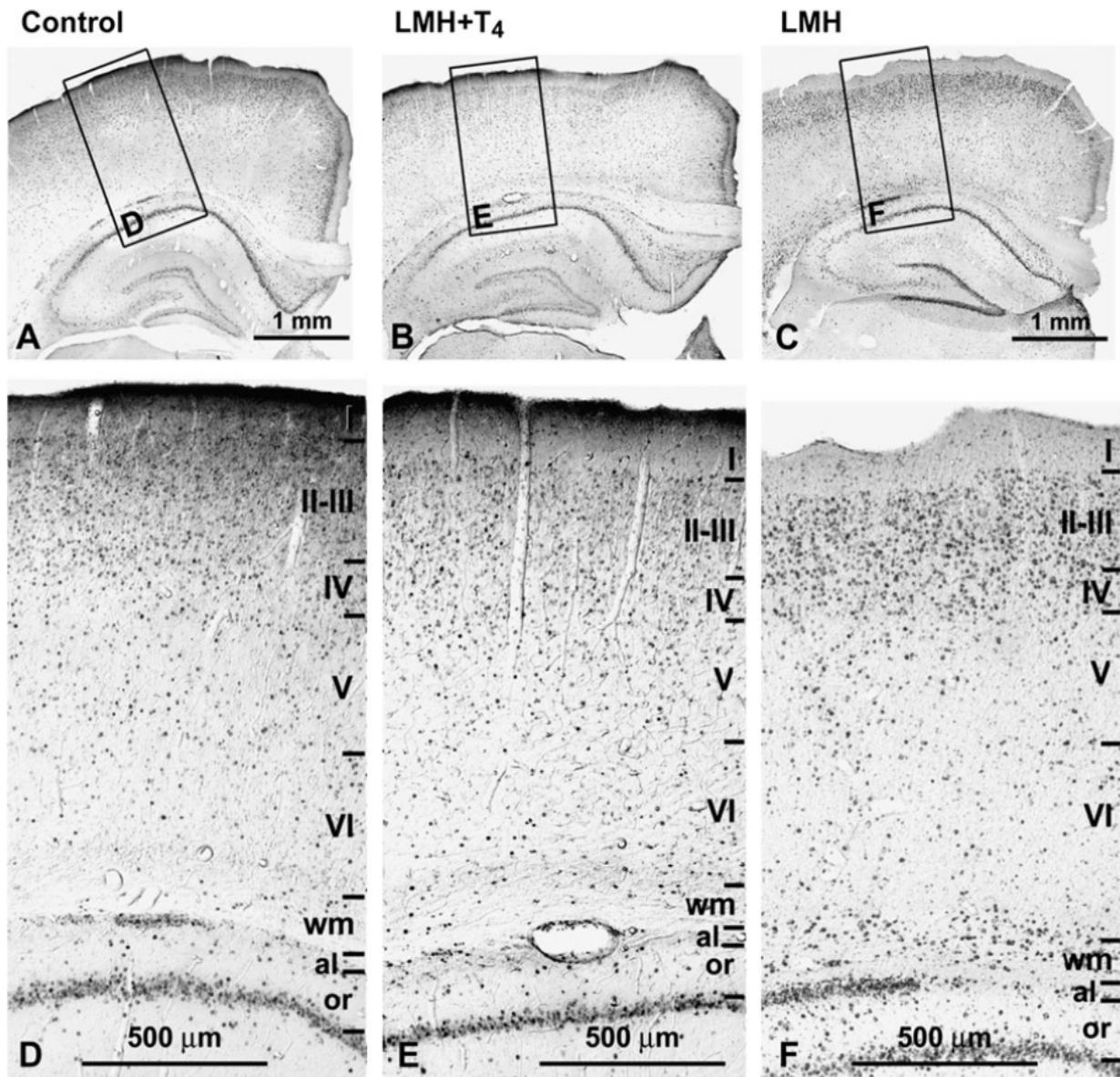


Fig. 3. (A–C) Low-magnification photomicrographs of coronal sections of the parietal cortex and hippocampus showing BrdU-immunoreactive cells after E17–20 injections in control, LMH þ T₄, and LMH pups at P40. (D–F) Details (boxes in A, B, and C) showing that both in layers I–VI and white matter (wm) the neocortex and the alveus (al) and stratum oriens (or) of the hippocampus, the radial distribution of BrdU-immunoreactive cells is more widespread in LMH pups than in control and LMH þ T₄ pups. Note the increased number of heterotopic BrdU-immunoreactive cells in wm, al, and or in LMH pups compared with that of control and LMH þ T₄ pups. The borders between layers are indicated by horizontal lines. LMH= Late maternal hypothyroidism. (Berbel P et al. *Cerebral Cortex* 2010)⁶⁰

6.2 Abnormal cortical cytoarchitecture and connectivity

Any situation compromising maternal thyroid hormone transfer to the fetus will disturb the neuronal migration process. As a result, neurons will not reach their final destination in the upper layers and their abnormal positioning will cause alterations in the laminar architecture of the cerebral cortex.⁴⁴

In biopsies performed in experimental animals maternal thyroid hormone deficiency was found to cause permanent and irreversible lesions in the cerebral cortex cytoarchitecture. As in gestational hypothyroidism, hypothyroxinemia causes neocortical layering blurred.

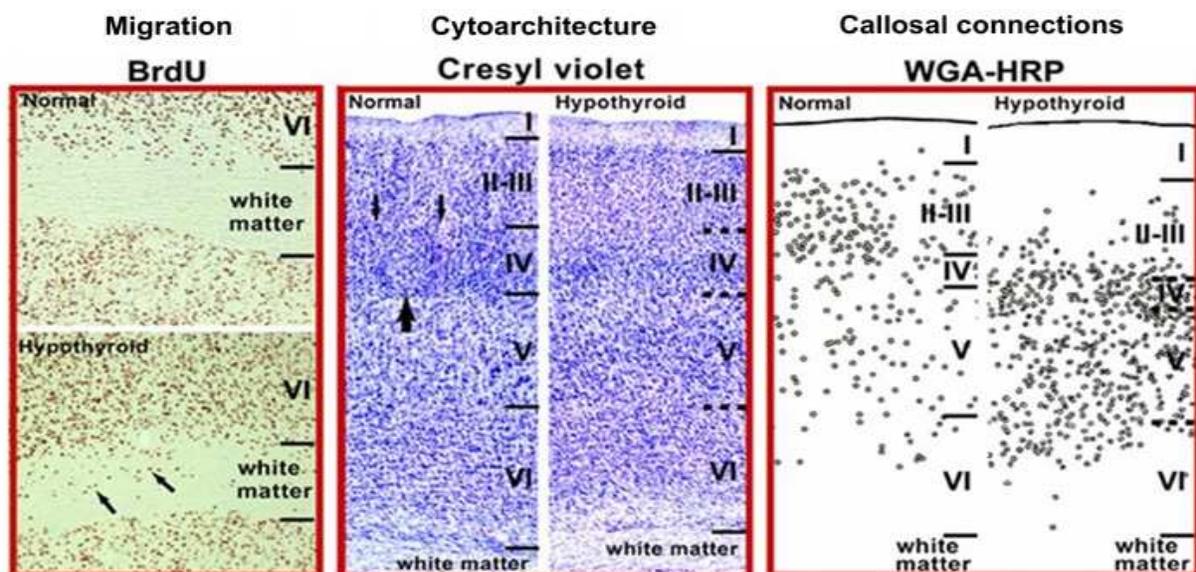


Fig. 4. **Left.** Photomicrographs of S1 coronal sections from normal and hypothyroid rats, showing the distribution of BrdU-labelled cells at P40, following injections at E15 and E17. Cells are more widely distributed in hypothyroid rats. Note the increased number of labeled cells, with respect to normal, in the white matter (wm) of hypothyroid rats.

Centre. Photomicrographs of cresyl violet-stained coronal sections showing the PMBSF cytoarchitecture and layer borders in normal and hypothyroid rats. In normal rats, borders between layers are clear cut, while in hypothyroid rats (dashed lines) they are blurred. Note that in layer IV of hypothyroid rats, instead of normal barrels, disperse patches of high cell density can be seen. Arrowheads point to two septae adjacent to the barrel indicated by the arrow. **Right.** Plots of retrograde-labeled callosal neurons are shown in normal and hypothyroid rats. In normal rats, an important proportion of labeled neurones are in supragranular layers II and III. On the contrary, in hypothyroid rats, almost all labeled neurones are between layers IV and VI (Berbel P. et al.

Neuroscience 2001)⁶².

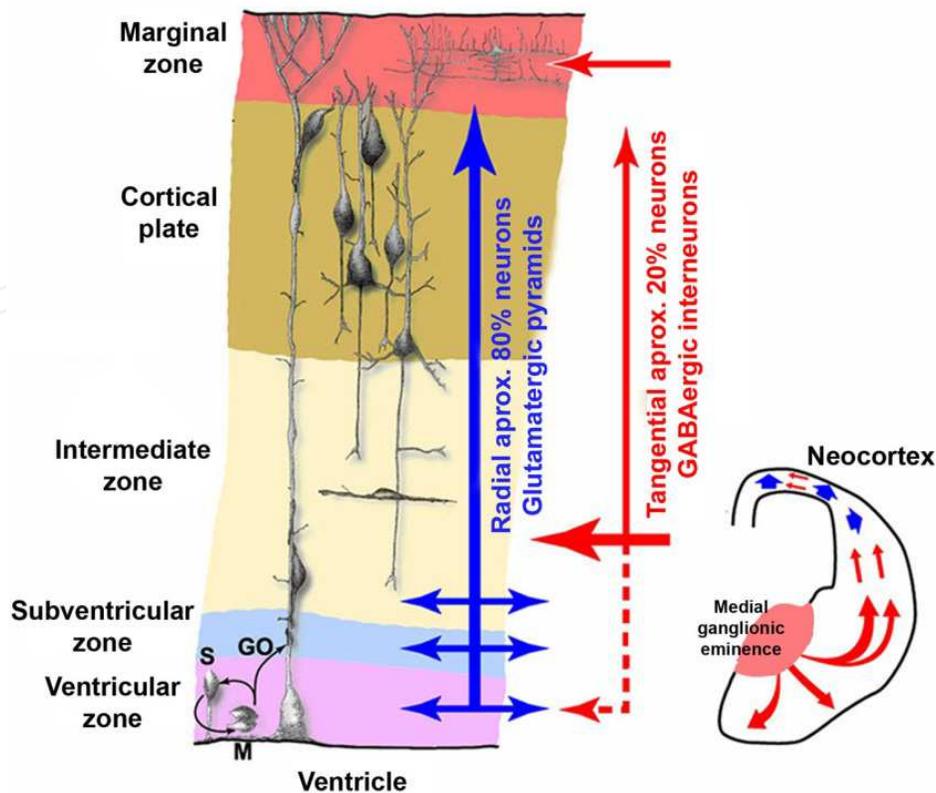


Fig. 5. Thyroid hormones play an important role in the neuronal migration process. Specifically, rats born to females with moderately low thyroid hormone levels have a disorganized cortical plate and many neurons do not migrate to their normal position. Furthermore, this action of thyroid hormones occurs during early fetal life. The figure shows the radial (blue arrow) and tangential (red arrows) migratory pathways. Both are affected by maternal hypothyroxinemia resulting in abnormal cortical lamination. (Adapted from *Berbel P. Mente y Cerebro* 2003)⁶³

7. Physiopathology of fetal cerebral damage

Within this broad framework, three different situations can be found, with different results:

When maternal hormone transfer is deficient –as in cases of maternal hypothyroidism or hypothyroxinemia–, the hormone concentrations transferred to the embryo and the fetus are inadequate during early pregnancy. Later, at the onset of fetal thyroid function, there is increased secretion of T4 and T3 by the fetal thyroid gland, though it fails to meet successfully the early disruption of maternal hormone supply. Thus, T4 and T3 concentrations in fetal tissues are fairly normal when the fetus reaches term, but its intrauterine development will have suffered alterations.^{38,64}

However, as the secretion of thyroid hormones increases, the fetal thyroid cannot store them. Therefore, neonates to mothers with thyroid malfunction have higher difficulty to meet the hormonal needs at birth than neonates to mother with normal thyroid function. This situation can lead to permanent neurological abnormalities^{38,40}.

When the maternal thyroid function is normal, but the fetal function is not –as it is the case in congenital hypothyroidism–, maternal T4 and T3 supply can partly mitigate fetal hypothyroidism. Although maternal T4 supply cannot replace completely the fetal thyroid

function, it is crucial for brain development, where it does maintain normal T3 concentrations. However, such concentrations are not maintained in other tissues at normal levels.⁶⁵

However, although maternal T3 levels are normal, this does not mitigate T3 deficiency in the fetus. The reason is that the fetal brain is totally dependent on the conversion of T4 into T3 by local action of 5'D-II, as T3 cannot be taken directly from plasma.^{38,66}

Thus, these findings prove that maintaining adequate T4 levels in the mother is crucial, as it protects the brain of fetuses with congenital hypothyroidism until birth. Conversely, although the mother has normal T3 concentrations maintaining maternal euthyroid status, this hormone does not protect the fetal brain in mothers with hypothyroxinemia^{38,40}.

When both the maternal and the fetal thyroid function are abnormal –as in the case of chronic iodine deficiency– mothers have very low levels of T4, though T3 concentrations are normal. In this situation, embryos and fetuses have deficient T4 levels during gestation and become increasingly deficient in T3.^{64,67}

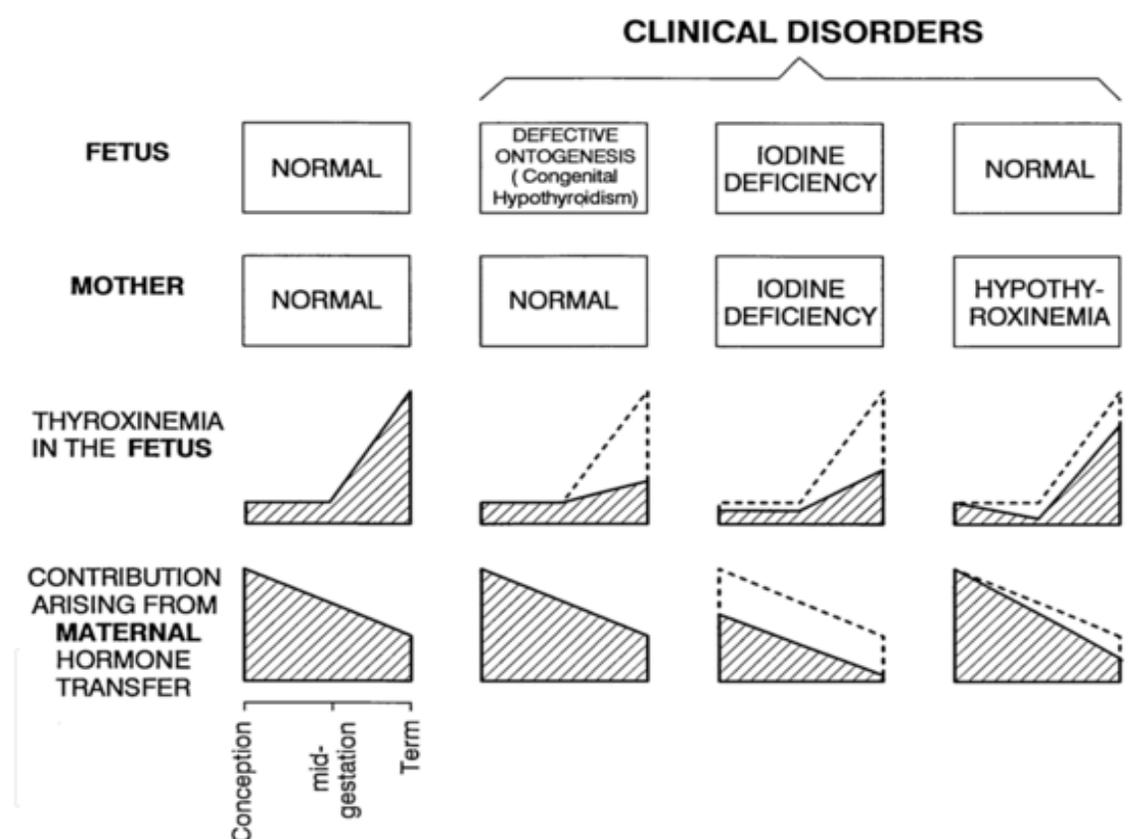


Fig. 6. In this table, the three clinical situations leading to altered maternal and/or fetal thyroid function are shown. It shows how the relative contributions of an altered maternal and/or fetal thyroid function can lead eventually to alterations in fetal thyroxine levels during intrauterine development. (From Glinoe D, Delange F. *The potential repercussions of maternal, fetal and neonatal hypothyroxinemia on the progeny*. *Thyroid* 2000, 10 (10): 871-887)⁶⁴.

When the fetal thyroid gland should start working, it cannot compensate for the disrupted maternal supply, since it does not have enough iodine for the synthesis and secretion of T4. At the same time, the fetal brain has not preferential protection from maternal T4, as this hormone cannot be biosynthesized due to the deficiency of iodine. As a result, fetal tissues –

including the fetal brain- are very deficient in T4 and T3 during very important stages of cerebral neurogenesis and maturation.^{41,68}

These data suggest that the pathogenic mechanisms that lead to cretinism and severe hypothyroidism are multifactorial, and the effects of severe iodine deficiency can be amplified by the deleterious effects of thiocyanate overload, selenium deficiency, and glandular destruction and fibrosis occurring gradually during childhood⁶⁹. By contrast, when iodine supplementation is given to women in regions with endemic iodine deficiency, cretinism can be eradicated, and neonatal hypothyroidism prevented⁷⁰.

8. Clinical effects of prenatal iodine deficiency

Now that we know the "virtually universal" participation of thyroid hormones in the development and proliferation of fetal neural tissue, the complex clinical manifestations of thyroid hormone deficit in early pregnancy can be easily anticipated.

Therefore, maternal and fetal hypothyroxinemia caused by iodine deficiency determines permanent lesions in the upper cortical areas, hippocampus and cerebellum^{48,64}, which causes neurological abnormalities with relatively well-defined characteristics:

- Brain stem or medullar elements are not affected, so there is no direct motor dysfunction, but abnormal motor coordination function³⁹.
- The lesions affect the integration areas of the cerebral cortex -including "silent" areas of the association areas of the cortex- showing poorly defined anatomical alterations.
- They do not have perinatal clinical expression, although they express later during early years of life until school age.^{71,72}
- Therefore, these lesions cannot be detected by modern prenatal diagnosis techniques.³⁰

A number of research studies conducted in regions with moderate iodine deficiency have shown the presence of irreversible alterations in the intellectual and neuro-psycho-motor development of infants and adults that were clinically euthyroid and that did not exhibit other signs or symptoms of endemic cretinism, which is the most serious form of brain damage caused by iodine deficiency.

In follow-up studies on infants of mothers with hypothyroxinemia identified in the first trimester of pregnancy, low scores were obtained on scales measuring psychomotor development (psychometric tests used to find evidence of these abnormalities are varied and include adapted intelligence tests, regardless of the subjects' culture). Such results were especially significant in those tests that assess visual-motor coordination, object manipulation, understanding the relationship between objects, imitation and early language development^{38,73}. The results showed low visual-motor performance, motor skills, perceptual and neuromotor skills, and low development and intelligence quotients (IQ)^{71,76}.

*Bleichrodt and Born*⁷⁴ conducted a meta-analysis of 19 studies on neuromotor and cognitive functions in conditions of moderate to severe iodine deficiency, and concluded that iodine deficiency leads to a loss of 13.5 IQ points, as compared with the global population. Apart from goiter, brain damage and loss of intellectual potential caused by iodine deficiency are an obstacle to the socioeconomic development of people, and must be considered as a major public health problem.

More recently, iodine deficiency -maternal hypothyroxinemia- has been identified as a causal factor of attention-deficit hyperactivity disorder⁷⁵.

9. Fetal and neonatal effects of iodine deficiency²⁷

Reference	Inclusion criteria	Conclusions	Comments
<p>Pharoah POD, Buttfeld IH, Hetzel BS.</p> <p>Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy</p> <p>Lancet 1971, 1: 308</p>	<p><i>Type of participants:</i> Total population from 27 villages in Papua Nueva Guinea.</p> <p><i>Type of intervention:</i> Administration of intramuscular iodized oil.</p> <p><i>Type of results:</i> Changing incidence of endemic cretinism</p>	<p>Controlled clinical trial in a city of 8,000 inhabitants.</p> <p>Intramuscular iodized oil is effective for the prevention of endemic cretinism. To be effective, it must be administered before conception.</p> <p>Maternal severe iodine deficit causes neurological damage during fetal development.</p>	<p>Pioneer intervention study on populations with severe iodine deficit.</p> <p>The cohort monitored is very small, as compared with the initial group.</p> <p>The results obtained are expressed in terms of infant mortality and endemic cretinism incidence.</p>
<p>Thilly C, Delange F y cols.</p> <p>Fetal Hypothyroidism and maternal thyroid status in severe endemic goiter</p> <p>J Clin Endocrinol Metab 1978; 47: 354</p>	<p><i>Type of participants:</i> A total of 109 pregnant women and 128 newborn babies from Ubangi, Zaire.</p> <p><i>Type of intervention:</i> Administration of intramuscular iodized oil to a group of pregnant women.</p> <p><i>Type of results:</i> Changing TSH, T4 and T3 concentrations in mothers and newborn babies.</p>	<p>Maternal thyroid function in regions with severe endemic goiter is a good indicator of the thyroid function in a neonate.</p> <p>The factors responsible for this hypothetical relationship seem to be environmental factors acting simultaneously in the mother and the fetus.</p>	<p>Pregnant women were grouped “randomly” into two groups.</p> <p>The results obtained are shown in thyroid function values of the mother and the neonate at birth.</p>
<p>Bleichrodt N, Born MP.</p> <p>A metaanalysis of research on iodine and its relationship to cognitive development.</p> <p>Nutr Rev 1996; 54 (4 Pt 2): S72- S78</p>	<p><i>Type of participants:</i> Previous Articles</p> <p><i>Type of intervention:</i> Metaanalysis of 19 studies on neuro-motor and cognitive functions under conditions of moderate to severe iodine deficiency.</p> <p><i>Type of results:</i> Depending on the study reviewed.</p>	<p>Iodine deficiency causes a decrease of 13.5 IQ points as compared with the global population.</p>	

Reference	Inclusion criteria	Conclusions	Comments
<p>Haddow JE, Glenn MD y cols</p> <p>Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child</p> <p>N Engl J Med 1999; 341: 549.5556</p>	<p><i>Type of participants:</i> 62 pregnant women with TSH above the 98th percentile, and 124 pregnant women with normal TSH levels.</p> <p><i>Type of intervention:</i> Infants aged 7-9 underwent 15 tests.</p> <p><i>Type of results:</i> Scores obtained in different neuropsychological performance tests.</p>	<p>Infants of women with high TSH concentrations scored seven points lower than the infants of 124 control women (p=0,005) in the 15 tests employed, and 19 percent scored 85 or even lower.</p> <p>Undiagnosed hypothyroidism in pregnant women can damage the fetus.</p>	<p>Retrospective study on a bank of pregnant women serum collected for a period of three years.</p> <p>The results are expressed in terms of the scores obtained in intelligence, attention, language, reading skills, school performance and vasomotor development tests.</p>
<p>Pop VJ, Kuijpers JL y cols.</p> <p>Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy</p> <p>Clin Endocr 1999; 50: 149- 155</p>	<p><i>Type of participants:</i> 220 pregnant women and 220 infants at 10 months.</p> <p><i>Type of intervention:</i> Study of maternal thyroid function and evaluation of the neurological development of infants at 10 months of life.</p> <p><i>Type of results:</i> Scores obtained by children on the Bayley Scale of Psycho-motor development.</p>	<p>Low free T4 plasma concentrations during early pregnancy may be a relevant risk factor of mental retardation in the progeny.</p> <p>Free T4 concentrations are defined as an independent parameter for the neurological development of the progeny.</p>	<p>This is the first study to prove that low free TSH levels in apparently healthy women during early pregnancy increase significantly the risk of fetal neurological damage.</p> <p>Maternal TSH, fT and TPO antibodies are analyzed at the 12th and 32th week of gestation.</p> <p>Consequences at the 12th week and the rest of weeks of pregnancy.</p>
<p>Morreale de Escobar G, Obregón MJ y Escobar del Rey F.</p> <p>Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia?</p> <p>J Clin Endocrinol Metab 2000; 85: 3975- 3987</p>	<p><i>Type of participants:</i> Previous articles</p> <p><i>Type of intervention:</i> Systematic analysis of articles published on the effects of maternal hypothyroxinemia on the fetal neurological development</p> <p><i>Type of results:</i> Relying on the study reviewed.</p>	<p>Maternal hypothyroxinemia in the first trimester increases the risk of fetal neuropsychological damage.</p> <p>Maternal T4 is the sole source of thyroid hormone for the fetal brain during the first trimester.</p> <p>Normal T3 concentrations in the mother do not prevent from potential damaged caused by a low T4 supply</p>	<p>Through analysis of the main findings made in regions with severe iodine deficiency, in regions without iodine deficiency and in studies with experimental animals.</p> <p>Development of a unifying theory on the severity and frequency of neurological damage in the progeny of mothers with hypothyroxinemia, in contrast with mothers with hypothyroidism.</p>

10. Studies with potassium iodide supplementation

Finally, supplementation with potassium iodide (KI) from the early stages of pregnancy in pregnant women has proven to be a safe and effective method for preventing cognitive impairment associated with nutritional iodine deficiency.

Inclusion criteria	Subjects	Methods	Conclusion	Comments	Reference
Pregnant women from a moderate iodine deficiency area.	Pregnant women treated with iodized salt compared with pregnant women as control group.	<p>Randomized Clinical Trial: 35 pregnant women of which 17 were administered 120-180 µg of iodine in form of iodized salt. Another 18 women served as the control group.</p> <p>Determination of TSH, Urinary iodine excretion (UIE) and thyroid volume.</p>	<p>Iodine Urinary Excretion in the third trimester was significantly higher in the group studied (100± 39 vs 50±37 of iodine). ($p<0,0001$)</p> <p>The thyroid volume increased significantly in the control group, mainly due to relative iodine deficiency.</p>	<p>Very limited sample size. The results obtained are statistically significant, although the sample size was very small. The authors suggest the use of iodine prophylaxis to prevent the increase in thyroid volume and avoid the risk of maternal and fetal hypothyroidism.</p>	Romano R, et al, Am J Obstet Gynecol 1991.
<p>Healthy pregnant women, recruited at early gestation.</p> <p>Exclusion criteria: thyroid disease or medication that could affect thyroid function</p>	Pregnant women treated with potassium iodide (KI) solution compared with pregnant women as control group.	<p>Randomized Clinical Trial: 28 pregnant women who received 200 µg/day of iodine from 17-18 weeks of gestation until 12 months after delivery. A total of 26 women served as the control group.</p>	<p>A relatively low iodine intake during pregnancy leads to thyroid stress, with increased release of TG and of thyroid volume, with little clinical effects, according to the authors.</p> <p>Iodine does not cause significant changes in T4, T3 or free T4 in serum.</p>	<p>Very small sample. The conclusions can not be considered as definitive. The same group presented seven years later a study with opposite results.</p>	Pedersen KM, Laurberg P and cols; J Clin Endocrinol Metab 1993

Inclusion criteria	Subjects	Methods	Conclusion	Comments	Reference
Euthyroid pregnant women, selected at the end of the first trimester with biochemical criteria of excessive thyroid stimulation (thyroglobuline ↑, with a low normal free T4 index and/or increased T3/T4 ratio.	Study with a control group and two groups that received 100µg/day of iodine and the other 100 µg/day of iodine+ 100 µg/day of T4. N=60 pregnant women in each group.	Randomized clinical trial, double-blind: In both groups of women who received active treatment, alterations in thyroid function associated with pregnancy improved significantly. Maternal and neonatal parameters of thyroid function, UIE and thyroid volume were assessed by ultrasound	The administration of T4 failed to mask the beneficial effects of iodine supplementation in pregnant women, especially in the prevention of goiter.	As a starting point, the researchers selected a population at risk relying on biochemical parameters indicating thyroid overstimulation. The results can not be extrapolated to normal populations of pregnant women.	Glinoe D et al, J Clin Endocrinol Metab 1995
Healthy pregnant women at 10-12 weeks of gestation.	Clinical trial , pregnant women who received IK were compared with a control group.	Non randomized clinical trial with 108 women, of whom 38 received 300 µg of IK/day (230 µg of iodine) and 70 served as the control group. Thyroid volumen, thyroid function, UIE and TPO antibody levels were measured in the week 10-12 and after delivery.	After receiving iodine fortification, IUE increased significantly in mothers and neonate The thyroid volumen in neonates to mothers that received fortification was lower than that of the control group	Iodine supplementation during pregnancy in regions with moderate iodine deficiency causes a lower thyroid volume in neonate. This supplementation does not increase TPO antibody frequency	Liesenkötter KP et al. Eur J Endocrinol 1996

Inclusion criteria	Subjects	Methods	Conclusion	Comments	Reference
Pregnant women, entering the study at any stage of pregnancy.	Clinical trial with pregnant women treated with IK and compared with a control group.	Non randomized and comparative study in pregnant women, of whom 93 received 150 µg/day of iodine and 419 served as control group. Determination of UIE and T4L during pregnancy, anti-TPO, anti-TG, maternal and neonatal thyroid volume	Iodine supplementation enhances significantly IUE and T4L levels during the whole gestation. Lower maternal and neonatal thyroid volume was found in the group that received supplementation.	The control group consisted of a significant sample of pregnant women. In both groups UIE increases progressively during pregnancy, but the control group had normal urinary iodine excretion <100 mg / L during pregnancy.	De Santiago J, et al J Endocrinol Invest 1999
Mother/newborn pairs. All newborns were healthy and delivered at term and were breastfed.	Babies from mother treated with IK compared with babies from a control group	Randomized clinical trial in 89 mothers and their babies: 57 served as the control group, 32 received 175 µg IK/day (134 µg of iodine) during pregnancy. Identification of thyroid volumen UIE, nutritional questionnaire	UIE of neonates to supplemented mothers increased by 62 percent, while the thyroideal volume of these children decreased by 18 percent, as compared with the control group. Neonatal TSH was maintained within normal ranges.	It DOES NOT include maternal thyroid function values. In this study, the fact that the mother was a smoker was taken into account. Babies born to smoking mothers had 20 percent higher thyroid volume than those born to non smokers.	Klett M et al Acta Paediátrica Suppl 1999

Inclusion criteria	Subjects	Methods	Conclusion	Comments	Reference
Healthy pregnant women with no previous history of thyroid disease were recruited when admitted for delivery.	Pregnant women that have taken IK were compared with a control group. Babies from mother treated with IK compared with babies from a control group	Observational study 144 women and their progeny participated in the study, of which 49 received 150 µg iodine/day during pregnancy and 95 served as control subjects. Identification of maternal thyroid function (TSH, T4L, T3L, TG) and neonatal function in cord blood (TSH, T4L, T3L, thyroglobulin)	Researchers found that TSH has an opposite behavior in the mother (decreases) to that of the neonate (increases) in the group supplemented with iodine. T4L is higher in the mothers and infants of the supplemented group.	The authors attribute the rise in TSH to a transient impasse of neonatal iodine-induced thyroid.	Nøhr S, Laurberg P
TPO-Ab-positive women in early pregnancy	Three groups of study stratified by anti-TPO titers into 3 groups: 22 women received 150 mg iodine / day from conception up to 9 months postpartum (+/+), only 24 received iodine during pregnancy and 26 (+/-) did not receive iodine (-/-).	Placebo-controlled, randomized, double blind trial. Study of thyroid function at 35 weeks of gestation and 9 months after delivery.	They found that the incidence, severity and type of thyroid dysfunction postpartum rely predominantly on anti-TPO levels (positive correlation). Supplementation with iodine during pregnancy and postpartum does not induce or worsen postpartum thyroid dysfunction.	The authors concluded that iodine supplementation during pregnancy and postpartum is safe, even in women with positive anti-TPO. Screening for anti-TPO in the first trimester can predict women at risk of developing postpartum thyroid dysfunction.	Nøhr S, et al J Clin Endocrinol Metab 2000

Inclusion criteria	Subjects	Methods	Conclusion	Comments	Reference
Pregnant women enrolled from the 10 th to the 16 th week of gestation.	32 pregnant women supplemented with 50 µg/day of iodine (group A) and 35 received 200 µg/day (group B) from conception to 6 months after delivery.	Randomized clinical study Determination of thyroid volume, thyroid function in all three trimesters of pregnancy.	The dose of 50 µg/day is an inexpensive and safe method to prevent goiter. The dose of 200 µg/day seems to be more effective, has not side effects and does not increase the frequency of autoimmune postpartum thyroiditis.	There were not any control group, since the Committee of Ethics and Clinical Research did not give authorization. Five cases of postpartum thyroiditis (2 in group A and 3 in group B) were detected. All these women had low circulating autoantibodies before starting the test.	Antonangeli L et al Eur J Endocrinol 2002
Children whose mothers were supplemented during pregnancy. The comparison group were children recruited at 2 years of age.	148 infants of mothers who received iodine supplementation during pregnancy were compared with 169 infants who received iodine aged from 2 years, for a period of 1 year. There were no untreated group.	Longitudinal study. Psychometric tests used: Raven Progressive Matrices, Developmental test of Visual Motor Integration (VMI) and Denver Developmental Screening Test (DDST).	Iodine before the 3 rd trimester predicted higher psychomotor test scores for children relative to those provided iodine later in pregnancy or at 2 years of age.	Iodine supplementation was carried out by adding it to the irrigation water.	O'Donnell K, et al Develop Med & Child Neurol 2002
Pregnant women at the first trimester of gestation for the study group. Pregnant women at the third trimester of gestation for control group.	The study included 133 women who received 300 µg of potassium iodine and 61 women who had received no iodine supplements.	Non randomized, clinical trial. Main outcome measures: Bayley Scales of Infant Development. Maternal and infant thyroid function: TSH, free T3, free T4 and urine iodine	Infants whose mothers had received an iodine supplement had more favorable psychometric assessment and higher scores on the Psychomotor Development Index ($p = 0,02$) and the Behavior Scale.	Given the possible presence of confounding variables not controlled for in this study, these findings should be considered as preliminary.	Velasco I et al J Clin Endocrinol Metab 2009;

Inclusion criteria	Subjects	Methods	Conclusion	Comments	Reference
<p>Group 1 included infants of women with FT4 above the 20th percentile at 4-6 gestational weeks and at full-term.</p> <p>Group 2 included neonates to women with mild hypothyroxinemia diagnosed during the first 12-14 gestational weeks and with FT4 above the 20th percentile at full-term.</p> <p>Group 3 included infants born to women with mild hypothyroxinemia without iodine supplementation during pregnancy.</p>	<p>Three groups of infants were compared. Women of all groups were iodine supplemented from the day of enrolment until the end of lactation.</p>	<p>Clinical trial</p> <p>Psychometric Test: Brunet-Lézine Scale at 18 months of age.</p>	<p>Delayed Neuro-behavioral performance was observed in 36.8 percent and 25.0 percent of infants in groups 3 and 2, respectively, as compared with infants in group 1.</p> <p>A delay of 6-10 weeks in iodine Fortification of Hypothyroxinemic mothers at the beginning of gestation increases the risk of neurodevelopmental delay in the progeny.</p>	<p>Women of all groups were iodine supplemented (200 µg KI per day) from the day of enrollment until the end of lactation.</p> <p>No women were found to be Hypothyroxinemic at full-term after supplementation.</p>	<p>Berbel P, et al. Thyroid 2009</p>

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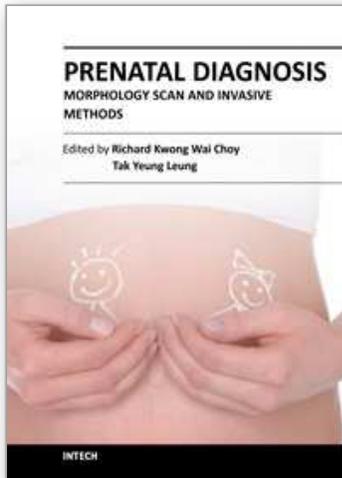
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This book provides detailed and comprehensive coverage on various aspects of prenatal diagnosis-with particular emphasis on sonographic and molecular diagnostic issues. It features sections dedicated to fundamentals of clinical, ultrasound and genetics diagnosis of human diseases, as well as current and future health strategies related to prenatal diagnosis. This book highlights the importance of utilizing fetal ultrasound/clinical/genetics knowledge to promote and achieve optimal health in fetal medicine. It will be a very useful resource to practitioners and scientists in fetal medicine.

How to reference

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