Gynecological Endocrinology, ~~May 2007; 22(5): 1–15~~

informa
healthcare

ORIGINAL ARTICLE

Iodine and thyroid hormones during pregnancy and postpartum

FAUSTINO R. PÉREZ-LÓPEZ

Department of Obstetrics and Gynaecology, University of Zaragoza Faculty of Medicine, Zaragoza, Spain

(Received 14 March 2006; revised 18 May 2007; accepted 21 May 2007)

Abstract

Iodine is a trace element essential for synthesis of the thyroid hormones, triiodothyronine and thyroxine. These hormones play a vital role in the early growth and development stages of most organs, especially the brain. The World Health Organization (WHO) has declared that, after famine, iodine deficiency is the most avoidable cause of cerebral lesions including different degrees of mental retardation and cerebral paralysis. The main function of iodine in vertebrates is to interact with the thyroid hormones. During pregnancy sufficient quantities of iodine are required to prevent the appearance of hypothyroidism, trophoblastic and embryonic or fetal disorders, neonatal and maternal hypothyroidism, and permanent sequelae in infants. Thyroid hormone receptors and iodothyronine deiodinases are present in placenta and central nervous tissue of the fetus. A number of environmental factors influence the epidemiology of thyroid disorders, and even relatively small abnormalities and differences in the level of iodine intake in a population have profound effects on the occurrence of thyroid abnormalities. The prevalence of disorders related to iodine deficit during pregnancy and postpartum has increased. Iodine supplementation is an effective measure in the case of pregnant and lactating women. However, it is not implemented and the problem is still present even in societies with theoretically advanced health systems. During pregnancy and postpartum, the WHO recommends iodine intake be increased to at least 200 μg/day. Side-effects provoked by iodine supplementation are rare during pregnancy at the recommended doses.

Keywords: *Iodine, thyroid hormones, triiodothyronine, thyroxine, fetal health, iodine deficit, pregnancy, fetal growth, brain development*

Introduction

Minerals and vitamins are micronutrients which have a pivotal function throughout the many stages of a woman's life, particularly during pregnancy and breastfeeding. The effect of improper nutrition is influenced by gestational age, severity of deficiency, or both. Among the trace elements necessary to aid reproduction are iodine, iron, zinc and copper [1]. Iodine has played a significant role in animal evolution; Neanderthal man had physical features similar to those of the present-day human with cretinism [2]. The ability of the thyroid gland to extract and use iodine, and changes in the transportation capacity of thyroid hormones, have been postulated as part of the driving force of human evolution [3,4]. The first references to goiter – a sign of iodine deficiency – in *Homo sapiens* date back some 5000 years in China and 3000 years in India. Approximately 3500 years ago the Chinese used seaweed to reduce the size of goiters. In the 1830s, the Frenchman Boussingault first identified that the use of salt with iodine achieved a good standard of health in people living in the mountainous Andean regions, after observing the absence of goiter in the lowlands of Colombia where a natural salt obtained from the iodine-rich waters of an abandoned mine was consumed. The use of iodine salt extended throughout Europe, but administration of high doses provoked the appearance of side-effects and its use was discredited.

In its natural form, iodine can be found dissolved in seawater and in marine plants, although it is also found in some minerals and in soil. In vertebrates its only clearly established function is the synthesis of thyroid hormones. A deficiency of iodine provokes a wide range of disorders (Figure 1) including endemic goiter, hypothyroidism, cretinism, decreased fertility, miscarriage, increased infant mortality and mental retardation (Figure 2). Using figures from the World Health Organization (WHO), the European

Correspondence: F. R. Pérez-López, Department of Obstetrics and Gynaecology, University of Zaragoza Faculty of Medicine, Domingo Miral s/n, Zaragoza 50009, Spain. Tel: 34 976 76 1734. Fax: 34 976 76 1735. E-mail: gine@unizar.es

ISSN 0951-3590 print/ISSN 1473-0766 online © 2007 Informa UK Ltd.
DOI: 10.1080/09513590701464092

Commission estimates that iodine deficiency puts 2.2 billion people at risk worldwide [5]. Steps taken to control iodine deficiency have proved to be highly cost-effective as national interventions. The United Nations-sponsored Declaration for the Survival, Protection and Development of Children maintains that 'every child has the right to an adequate supply of iodine to ensure its normal development' [6]. However, iodine deficiency at critical stages of development in fetal life and early childhood remains the world's single most important and preventable cause of mental retardation [5]. It is worrying that in spite of the fact that iodine deficiency can be controlled by taking simple measures, it continues to pose a problem to public health at the beginning of the 21st century, even in the supposedly more advanced countries with a higher level of welfare. Despite its health implications, many pregnant women still do not receive the adequate supplement. Part of the problem arises from the lack of an effective policy with regard to the consumption of iodinated salt and part from ignorance on the part of the health professionals involved. This article reviews some recent scientific evidence on the significance of iodine and the thyroid hormones on fetal and maternal health.

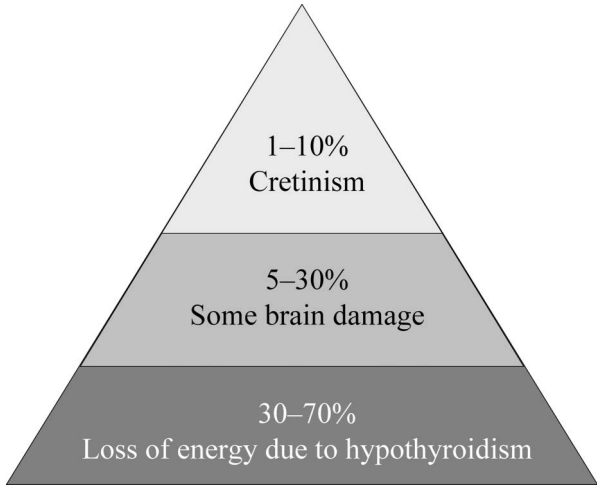

Figure 1. A pyramid showing that visible effects of iodine deficiency – goiter and cretinism – occur in 1–10% of cases, whereas the negative effects of iodine deficiency remain hidden in 90% of cases. Some childhood and adult brain damage, impairment of intellectual function, and loss of energy may be the expression of iodine deficiency and hypothyroidism.

Pathophysiology of iodine deficiency

Iodine is primarily obtained through the diet but is also a component of some medications, such as radiology contrast agents, iodophor cleansers and amiodarone. It is present in the superficial layers of soil and absorbed by crops grown on it. Its content in food and water depends on several factors such as geochemical conditions, altitude, fertilizers used, rainfall and microbes in the soil [7,8]. Glaciations, heavy snow and heavy rain leach away iodine from the soil. This problem is further accelerated by deforestation. The consumption of crops and plants grown on iodine-deficient soils leads to iodine deficiency in populations solely dependent on this vegetation for their iodine requirements. Ocean water contains amounts of iodine, and the great quantity of iodine contained in seaweed could partly explain the low prevalence of iodine insufficiency

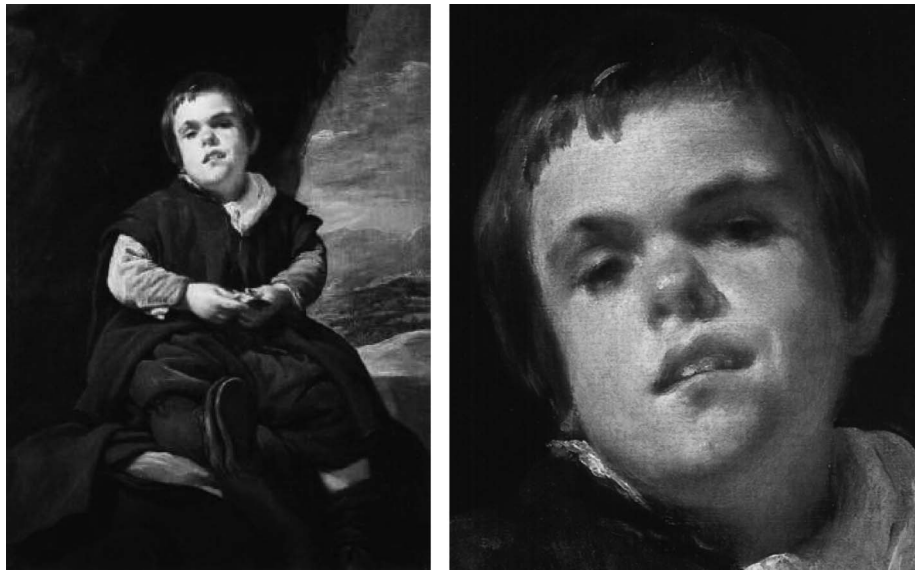

Figure 2. 'El Niño de Vallecas' (oil on canvas, 107 cm × 83 cm; 1643–45), by Diego Rodríguez de Silva y Velázquez (detail shown on the right). The subject is the dwarf Francisco Lezcano, who corresponded to a case of cretinism. During the 1630s and 1640s Velázquez painted a series of portraits of the dwarfs at court, playmates of the royal children, for they interested him as character studies. Museo del Prado, Madrid.

among people who consume large quantities of sea plants, such as the Japanese. Only people eating specific species of sea fish and sea products like seaweeds are more likely to be iodine-sufficient, but these are not accessible to everyone. The bacterial load of water, recurrent infections, and the ingestion of goitrogens present in foods such as cabbage, cassava, sweet potato and millet have also been identified as other etiological factors for an insufficient use of iodine. In the Western world, precooked dishes and fast foods do not guarantee the minimum quantity of iodine necessary for everyday life.

The iodine in food is assimilated in the digestive system; it then enters the bloodstream, and concentrates in the thyroid gland via an energy consumption mechanism. The sodium/iodide symporter (NIS) is an intrinsic plasma-membrane glycoprotein that mediates active iodide transport into the thyroid gland and into several extrathyroid tissues, in particular the lactating mammary gland. The symporter cotransports two sodium ions (Na^+) along with one iodide ion (I^-), with the transmembrane sodium gradient serving as the driving force for iodide uptake [9].

During pregnancy the renal clearance of iodine increases significantly due to the higher glomerular filtration rate [10]. The iodine loss in urine results in a compensating increase in thyroidal iodine clearance which can cause enlargement of the thyroid gland, the so-called 'pregnancy goiter'. Maternal thyroid volume, measured by ultrasound, increases during pregnancy in those regions where the iodine intake is low ($\approx$50 μg). Nevertheless, in those areas replete with iodine there is either no difference or only a slight increase in goiter prevalence or ultrasound-measured thyroid volume between pregnant and non-pregnant women [11–14]. A second mechanism for the reduction of iodine levels in the mother takes place in the late stage of the pregnancy, as a consequence of the transfer of maternal iodine to the fetoplacental unit. Some days after the end of pregnancy, iodine elimination in urine returns to pregestation values [14], possibly as a consequence of the normalization of renal iodine clearance or the disappearance of the placenta as well as the substances produced by this organ.

When the pregnant woman's diet does not contain a sufficient quantity of iodine, this can lead to hypothyroidism and goiter. In those regions where dietary iodine intake is borderline (50–100 μg/day), it would be necessary to increase the iodine intake during pregnancy and during the child's first year of life. During the 9 months of pregnancy, the thyroid iodine reserves are reduced by approximately to 40% and the thyroid enlargement is bigger with successive pregnancies [14]. This thyroid 'damage' could partly explain the preponderance of thyroidal disorders in the female sex. It remains to be proved if protection of the woman during the reproductive phenomenon – including breastfeeding – could somehow neutralize this aforementioned difference in terms of gender.

Perchlorate, nitrate and thiocyanate

Contaminants which alter the iodine metabolism in living beings are present in water. The effect of perchlorate has been known for a long time although its clinical relevance was ignored. It is a competitive inhibitor of the NIS that has been used as an oxidizer in solid rocket fuels, in explosives, road flares and pyrotechnics, and the chemical can also form naturally in the atmosphere. Its presence is so widespread that it has reached groundwater, drinking water, and foods including milk, vegetables, fruit, grains and forage crops [9,15]. In some regions of the USA, commercialized milk and breast milk have high levels of perchlorate. The perchlorate in cow's milk may be even higher in other countries than in the USA [16]. It is surprising to note that the average concentration in breast milk is five times higher than in dairy milk [17].

Nitrate and thiocyanate are also antithyroid agents acting at the NIS system level that might contribute to iodine deficiency in pregnancy. Nitrates are found in many food products, in green leafy vegetables, as a preservative for meat and fish, or as a contaminant as a consequence of the use of organic and mineral fertilizers. They are also present in river water and aquifers as a result of contamination from the aforementioned fertilizers. Though no iodine deficiency has been observed in people exposed to nitrate-contaminated water, a thyroid hypertrophy has been reported when the levels exceed 50 mg/l [18].

Thioglucosides found in certain plants, especially in the Brassicaceae family (cabbage, Brussels sprouts, cauliflower and broccoli), corn, apricots, cherries and almonds, are hydrolyzed by glucosidades in the gut and release free cyanide that is converted into thiocyanate. In certain African regions where cassava represents a major food staple, it has been associated with thiocyanate overload, aggravation of iodine deficiency during pregnancy and fetal hypothyroidism [19]. The concern is that the thiocyanate could reach newborn babies through breast milk or cow's milk-based formulas, and the iodine deficiency could get worse during the first postnatal months. In Europe, iodine deficiency has also been related to thiocyanate in breastfeeding mothers who smoke [20].

Dioxins and polychlorinated biphenyls

Dioxin and dioxin-like substances are often byproducts of industrial processes that should be considered highly toxic. The major source of human exposure is through the diet, since these substances are concentrated in the fatty tissues of meat, poultry,

pork and fish. Dioxin-like substances are also absorbed by the organism in significant quantities through smoking. Dioxins may alter thyroid function, especially during pregnancy [21,22]. In pregnant women exposed to polychlorinated biphenyl congeners, maternal triiodothyronine (T_3) levels are low, thyroid-stimulating hormone (TSH) levels in umbilical cord blood are high, and free T_3 (fT_3) levels are decreased [23]. More significantly, exposure in the uterus provokes a decrease in the intellectual capacity of the child after several years [24].

Iodine and thyroid hormones during pregnancy and the postpartum period

Thyroglobulin (TG) is the protein of the thyroidal matrix where the thyroid hormones are synthesized. It is a molecule without hormonal peripheral effects, which indicates thyroid gland activity. The thyroid gland synthesizes and releases thyroxine (T_4) and T_3, which are the only hormones that contain iodine in vertebrates. In the thyroid follicular cells, four iodine atoms are incorporated in each T_4 molecule and three in each T_3 molecule. T_4 is the main product of the thyroid secretion, and its deiodination to T_3 takes place in the peripheral target cells. Both T_4 and T_3 are linked to TG, which provides a matrix for their synthesis and a vehicle for their subsequent storage in the gland. In maternal blood over 99% of the thyroid hormones are transported attached to three proteins: thyroxine-binding globulin (TBG), transthyretin and albumin. TBG shows higher affinity towards the thyroid hormones and in spite of its low concentration is responsible for the larger part of the transportation of T_4 (68%) and T_3 (80%) [10,25]. The thyroid hormones can be released quickly from the transportation binding proteins, and consequently penetrate the target cells. The production of thyroid hormones is controlled by TSH, which is synthesized in the anterior pituitary gland in response to TSH-releasing hormone (TRH) secreted by the hypothalamus. Unbound or free T_3 (fT_3) and T_4 (fT_4) exert a negative feedback on the synthesis and release of TSH and TRH in order to maintain circulating thyroid hormone levels within the required range (Figure 3).

For a long time it was thought that thyroid hormones cross the cellular membrane of the target cells through a simple diffusion process, owing to its lipophilic properties. Currently, however, it is known that cell incorporation involves a carrier-mediated process. Two stereospecific binding sites for each of T_4 and T_3 have been identified and detected in the cell membrane of humans and other species. Cellular uptake of T_4 and T_3 by the high-affinity sites produces the translocation of thyroid hormones over the plasma membrane through a process which consumes energy and depends on temperature and Na^+ [11,16].

Several inorganic anion transporters and L-type amino acid transporters have been identified which facilitate translocation of the thyroid hormones from the plasma through the cell membrane and to the nucleus, where the specific receptors are located. The monocarboxylate transporter 8 (MCT8) has been characterized as the most specific and powerful T_3 transporter found, emphasizing a significant role for

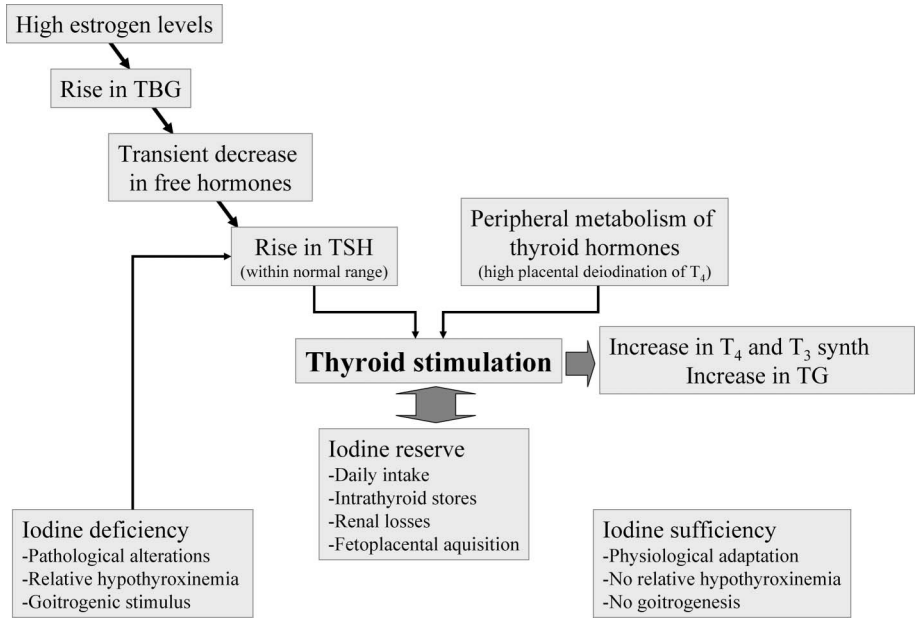

Figure 3. Thyroid homeostasis during pregnancy (TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone; T_4, thyroxine; T3, triiodothyronine; TG, thyroglobulin).

membrane transporters in the regulation of local T_3 action [12]. Furthermore, the importance of the cell membrane transport is supported by the discovery of a genetic mutation associated to an X-linked mental retardation syndrome characterized by neurological defects and a high T_3 without the skeletal and intestinal symptoms of hypothyroidism [13,14].

The action of thyroid hormones is performed via the thyroid hormone receptors (TRs), which belong to the superfamily that also includes the steroid hormone, vitamin D and retinoic acid receptors. In humans, four main TR isoforms ($\alpha1$, $\alpha2$, $\beta1$ and $\beta2$) have been described. TRs have a central DNA-binding domain containing two zinc fingers, a carboxy-terminal ligand-binding domain and a trans-activation site, as well as an amino-terminal domain with a poorly defined function [26]. They bind the ligand, T_3, with similar affinity and binding kinetics, with K_m values of 1–10 nM. T_3–TR complexes then bind to thyroid hormone response elements, which are specific DNA sequences. The functional TRs thus serve to promote or inhibit the transcription of thyroid hormone-responsive genes [27].

In healthy people thyroid function parameters vary depending on the individual, while the intra-individual variability is maintained within narrow margins [28]. This situation suggests that each subject has a determined thyroid adjustment according to genetic and environmental factors. The hereditary factors represent between ~26% and 65% of the variation in TSH, fT_4 and fT_3 out of the total variation among individuals [29,30]. Minimum alterations of the bioavailable thyroid hormones can have consequences that derive from a variety of clinical situations related to hyper- and hypothyroidism, subclinical hyper- and hypothyroidism, which can be shown in endpoints such as atherosclerosis, bone mineral density, obesity and heart rate [31].

Trophoblastic implantation and the placental Na(+)/I(−) symporter

Thyroid dysfunction and autoimmunity are prevalent in infertile women. The presence of positive thyroid peroxidase antibody is higher in infertile women than controls, and women with endometriosis present the highest prevalence of positive antibodies. Therefore, thyroid autoimmunity is significantly more frequent in infertile women than in healthy fertile controls [32]. Thyroid hormones have also been linked to miscarriage and maternal age. Recent studies have shown an association between thyroid autoimmunity and the risk of spontaneous abortion [33]. The overall risk of miscarriage was 2.4%, with the risk significantly higher among women over 35 years of age. Women with mild thyroid dysfunction at early gestation stages are frequently treated with T_4 to prevent obstetric complications, although there is no randomized clinical study to support this practice. Furthermore, it seems that thyroid antibodies in euthyroid women do not influence the results obtained with *in vitro* fertilization–embryo transfer techniques [34]. However, in threatened abortion with a live fetus, chorionic gonadotropin (hCG) was higher in women who do not abort than in women who miscarry, while serum fT_4 levels were lower and TSH higher in women with a negative outcome compared with women with a normal evolution of pregnancy [35].

During embryonic development, the trophoblast is not an inert tissue but plays a pivotal role in the regulation of iodine and thyroid hormone transfer from the mother. The development of the human placenta is a complex process that includes the proliferation and invasion of extravillous trophoblasts into the uterine decidua. The mechanism which transforms the extravillous trophoblast from a proliferative phenotype in cytotrophoblast columns into an invasive phenotype within the uterine tissues and spiral arteries is not well known, although it is suspected that the cytokines and growth factors produced locally are of great significance [36,37]. T_3 acts synergistically together with epidermal growth factor in the regulation of implantation [38,39]. The trophoblastic tissue and the decidua have a great nuclear capacity to link themselves to radio-labeled T_3, which is indicative that these tissues are sensitive to the active thyroid hormone. Furthermore, TRs are found in both the syncytiotrophoblast and the cytotrophoblast throughout the entire pregnancy [40].

The specific thyroid hormone transporter MCT8 is expressed in the placenta during all stages of pregnancy in the villous cytotrophoblast and syncytiotrophoblast [41], with a similar distribution to that of type III iodothyronine deiodinase (D_3) enzyme which turns the prohormone T_4 into active T_3. Inadequate placental development will result in a limitation of fetal intrauterine growth and in a gestational pathology.

The placenta assumes the passage of iodide and iodothyronines from mother to fetus, but the molecular mechanisms of this transport are not accurately known yet. Recently, transporters of the NIS expression in placental tissue at different gestational stages have been identified [42]. In the first trimester, a heterogeneous NIS immunoreactivity has been found in cytosyncytiotrophoblast cells, with a range of NIS-positive cells from 5% to 80%, in mesenchymal and endothelial cells from 1% to 40%, in decidual cells from 5% to 40%, and in endometrial glands from 3% to 40%. At the end of pregnancy, the results were very similar for the different areas studied. Although a large variation in NIS expression was observed from one sample to another, NIS expression was produced

predominantly in cytotrophoblast cells [43], suggesting that it may actively transport iodide from the villous syncytiotrophoblast layer, in contact with the maternal blood, toward the fetus. Moreover, the NIS expression appeared to be higher in cytotrophoblast cells obtained from a first-trimester placenta than in cells obtained from a term placenta.

Maternal thyroid hormones during pregnancy

The feedback mechanism of the hypothalamic–pituitary–thyroid axis functions normally during pregnancy if the iodine intake is of the required amount, although modifications to regulate basal TSH levels and modifications in response to this hormone induced by different stimuli [44–47] should also be considered. Several studies confirm that TG increases from the first trimester of pregnancy and later – particularly close to term – levels are even higher. At present, it is not recognized that hCG constitutes a stimulus to increase TG. Glinoer and colleagues [48] propose that TG alterations might be a biochemical marker to monitor the goitrogenic stimulus due to iodine deficiency during pregnancy. The total serum thyroid hormones T_4 and T_3 increase significantly during the first half of pregnancy. T_4 increases sharply between 6 and 12 weeks; then it experiences a slight increase reaching steadier levels around halfway through the pregnancy. In the case of T_3 the increase is more gradual. T_4 shows a higher affinity toward TBG than T_3. For that reason, the changes in T_4 have a higher parallelism with the changes in TBG. T_4 and T_3 reach a plateau at the beginning of the second trimester with values 30–100% higher than before pregnancy [49,50]. The main cause for the change in thyroid hormones is the increase in TBG concentration, and to a lesser extent the activity of placental D_3 which turns T_4 into reverse T_3 (rT_3) and T_3 into diiodothyronine (T_2). The growing need for T_4 and T_3 leads to an increase in their production.

The affinities of the three transport proteins are not altered during pregnancy; although TBG concentration is two or three times higher than that found in a non-pregnant woman, the other two do not vary significantly. TBG increases a few weeks after conception and reaches a plateau in the middle of pregnancy. The causes of this increase could be: (1) an increase in hepatic synthesis due to the placenta estrogenic stimulus; (2) an increase in trophoblastic production; and (3) an estrogens-induced increase in the proportion of TBG with a high content of sialic acid, which confers an extended average life, ranging from 15 min to 3 days in the case of the heavily sialylated TBG [39,51]. A third of the circulating TBG transports the T_4 molecule in the non-pregnant woman and the molar ratio of T_4/TBG is 0.35–0.40. During pregnancy the extrathyroid T_4 pool is increased in order to maintain homeostasis of the free hormone concentration, so that at the beginning of pregnancy the thyroid adjustment is continuous and T_4 and TBG levels constantly change. Consequently, during the first months of pregnancy, an adequate quantity of iodine is essential for the success of the new hormonal thyroid balance [50]. Once the first half of the pregnancy has been completed satisfactorily, thyroid hormone production stabilizes and a balance in the iodine consumption aimed at hormonal synthesis is achieved.

Results for fT_4 and fT_3 levels during pregnancy are controversial, the differences have been attributed to the measurement techniques [52] and to inter-individual variations which may be more evident during pregnancy than in non-pregnant women. At the end of pregnancy the free thyroid hormone levels are lower than or within the limits of the ones shown by non-pregnant women [49,53]. Difficulties are encountered in the study of free thyroid hormones due to the precision of the methodologies used. Roti and associates [52] have compared measurements of free T_4 and T_3 obtained using ten different methods and showed great variability of the results, although the free hormone values were always lower in pregnant women than in non-pregnant women. Using those methods not modified by changes in the serum levels of TBG and albumin, it is confirmed that at the moment of birth fT_4 levels are 10–15% lower than in non-pregnant women and fT_3 follows a similar pattern. Nevertheless, in many pregnant women the levels of free thyroid hormones are maintained within the range of non-pregnant women [54].

During pregnancy, iodine deficiency produces hypothyroxinemia which consequently causes (1) thyroid stimulation through the feedback mechanisms of TSH, and (2) goitrogenesis in both mother and fetus. In a pregnancy-serialized study, the thyroid hormones of pregnant women from a region with moderate iodine deficiency were compared with those of women coming from an area with sufficient iodine intake. T_4 decreased significantly in the first group compared with the second group between 29 and 36 weeks, and the TBG saturation and the iodine urinary excretion were significantly lower in women coming from the iodine-poor area. In both pregnant groups, fT_4 and T_3 decreased and values of fT_4 were significantly lower in the group coming from the iodine-poor area [55]. For this reason, it seems that moderate iodine deficiency causes an imbalance in maternal thyroid homeostasis, especially toward the end of pregnancy, leading to isolated hypothyroxinemia suggestive of biochemical hypothyroidism.

The chemical structure of hCG and biological tests suggest that it possesses the capacity to stimulate thyroid cells, although some of the evidence is circumstantial. Both hCG and TSH belong to the same family; they share the subunit α while the subunit

β provides them with specificity [56]. Trophoblastic tumors segregate hCG variants that might stimulate the thyroid gland *en masse*. Nevertheless, it is not known whether this extreme pathologic situation is relevant in the physiology of a normal pregnancy. *In vitro* studies offer conflicting results on thyroid cell stimulation with hCG. *In vivo*, the most relevant finding is that the increase of serum hCG temporarily coincides with the increase of thyroid hormones and the TSH decrease, indicating an inverse relationship between both hormones [49,57]. The action of hCG would hence ensure the contribution of an adequate provision of maternal thyroid hormones to the fetus at the stage of the pregnancy when fetal development, and particularly cerebral organogenesis, exclusively depend on the thyroid hormones provided by the mother [58]. During pregnancy, hCG concentration has been positively correlated to fT_4 ($r = 0.43$) and negatively to TSH ($r = -0.42$). Nevertheless, hCG administration does not alter fT_4 or TSH concentration [59].

During the third trimester of pregnancy, urinary iodine concentration and fT_4 were significantly lower in pregnant women than in non-pregnant ones, while the average TG was significantly higher than in the control group [60]. Three months after childbirth, thyroid stimulation was at maximum as shown by the significantly high levels of TSH and TG, and the reduction of urinary iodine and serum T_3 and fT_4 in comparison with controls. Nine months after childbirth values were similar in both groups of women. During the first postpartum months the decrease in maternal iodine levels is due to iodine elimination through breast milk, which contributes to maintaining homeostasis in the newborn. Consequently, it appears that the changes induced by pregnancy and breastfeeding can be corrected in the mother depending on the iodine levels in the diet. Nevertheless, these data should not give the impression that the mother is able to cover the iodine needs; on the contrary, they emphasize the need for iodine supplements during pregnancy and breastfeeding. The thyroid function of newborn babies in relation to the maternal thyroid status in the same population with a mild iodine deficit was studied, obtaining a maternal blood sample during the third trimester (32–39 weeks) and another sample right before childbirth; blood was also obtained from the umbilical cord at birth [61]. The average neonatal serum concentrations of TSH, TG and fT_4 were significantly higher than the corresponding maternal values. Conversely, the average maternal concentration of T_3 was significantly higher than the neonatal levels. The neonatal parameters did not differ between vaginal childbirth and Cesarean section. The fetal parameters showed significant correlations between TSH and fT_4 ($r = 0.4$), TG and T_3 ($r = -0.3$), and TG and fT_4 ($r = 0.5$). It can be interpreted that, in areas with a mild iodine deficit, fetuses are at the limit of decompensation as demonstrated by the increase of TSH and TG.

Fetal thyroid hormones during pregnancy

Thyroid development begins in the 10–12th week of gestation and is completed at the moment of birth; fetal T_4 is secreted from the 18–20th week onwards. Contrary to what was previously thought, maternal thyroid hormones reach the trophoblast and the embryo; T_4 has been measured in human celomic fluid during the 4th week of gestation and was detected in fetuses born without thyroid glands or suffering from thyroid dysgenesia [62,63]. The study of thyroid hormones in fetal blood in women under 14 weeks pregnant or between the 17th and 37th week of gestation in normal fetuses who were not affected by birth stress, showed that the T_4 transfer from mother to embryo is essential before the fetal hypothalamic–pituitary–thyroid system becomes operative [64]. This transfer is variable throughout gestation [39,62] and a relationship has been found between maternal and fetal levels during certain gestational periods [65,66]. The fetal thyroid grows between weeks 12 and 39 with the most pronounced increase during the second trimester, when the functional activity of the gland is more intense [67].

In the term gestation, the levels of TSH, TBG and all iodothyronines, except T_3, are higher than the values in non-pregnant women. During the third trimester, cord serum levels of fT_4, TSH, rT_3 and T_4 sulfate (T_4S) are higher than the corresponding maternal values, while fetal levels of T_4, T_3 and TBG are lower than the maternal ones [68]. The cord serum T_3 levels increase as the gestation advances, although the values – even in term gestation – are lower than those present in adults. These relatively low levels in fetal blood do not reflect the values present in the tissue which are high due to the active transport of this hormone through the cell membrane, the difference in fraction is linked to proteins in the intracellular and extracellular areas and mainly by local deiodination of iodothyronines [69,70]. Cord serum T_4 levels increase progressively during pregnancy, confirming the results previously obtained at different stages of pregnancy [71]. The cause of the increase in total thyroid hormones is the increase of TBG concentration and the production of D_3 in the placenta [50]. This enzyme is highly active during fetal life and turns T_4 into rT_3, and T_3 into T_2, in order to fulfill the demands of the bloodstream. The increase in T_4 and T_3 concentration is lower than expected with regard to the TBG increase, resulting in a condition of 'relative hypothyroxinemia' that is reflected by the decrease of fT_4 and by the progressive drop of the T_4/TBG quotient [53]. From the third trimester of pregnancy (2)

fetal levels of T_4 and TBG increase and the T_4/TBG quotient remains stable, coinciding with the concept that TBG maintains constant levels of fT_4.

TSH has been detected in fetal serum from the 11th gestational week [69]. Fetal TSH increases from week 15 until the end of the second trimester and then remains stable, decreasing slightly at the end of the pregnancy [68]. Levels of fetal rT_3 increase during the second trimester, reaching a peak at gestation week 25–30, and decrease during the third trimester and even further in the newborn after birth. These changes are related to the decrease in inner-ring deiodination of T_4 to rT_3 [72], which is of great significance in increasing the formation of T_3 after delivery. Sulfation has remarkable effects on the metabolism and homeostasis of iodothyronines. Once T_4 is transformed into T_4S it cannot be turned into the active hormone T_3, and can only be catabolized to rT_3S. Furthermore, sulfation accelerates the inner-ring deiodination of T_3 to T_2 [73]. Consequently, sulfation plays a significant role in regulating the amount of active thyroid hormone in the target fetal tissue.

Iodine and thyroid hormones during postpartum

Iodine is necessary during the first few months of life for neurological development and myelinization in order to achieve optimum intellectual development. Chan and co-workers [74] have studied the relationship between iodine and thyroid function during the first postpartum days (range of 3rd to 9th day) in 50 puerperal women and its relationship with the state of the neonate. Twenty-nine women presented a moderate iodine deficit (defined by urine iodine concentration <50 μg/l) and the average urine iodine content was 86.6 μg/g creatinine. The average iodine content in maternal milk was 84 μg/l; its milk concentration was significantly correlated to the iodine concentration in urine per gram of creatinine but it did not correlate with iodine in the urine expressed in μg/l. The values for TSH in neonates were significantly correlated to the high levels of iodine in breast milk.

During lactation the mother must receive enough iodine for the normal functionality of her thyroid gland and to maintain an adequate iodine quantity in her milk. It is estimated that some 114 μg iodine/day are lost via breast milk. The Panel on Micronutrients of the US Food and Nutrition Board [75] establishes 110 μg/day as a suitable intake for 0–6 month-old babies and 130 μg/day for 7–12 month-old babies. These proposals match the dose recommended by WHO, the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) [76]: 90 μg of iodine daily for infants between 0 and 59 months old.

Women who smoke have a lower quantity of iodine in their milk, although the quantity in urine does not differ between smokers and non-smokers [20], owing to the presence of high levels of thiocyanate that blocks the iodine transfer mechanisms. Despite the fact that artificial milk usually contains iodine quantities comparable to those in maternal milk, the urine excretion of iodine in infants nurtured with artificial milk indicates insufficient quantities or that the iodine content is present in such a way that it cannot be adequately absorbed [77].

The main cause of maternal postpartum thyroid dysfunction is postpartum thyroiditis (PPT), which is characterized by a brief phase of thyrotoxicity (1–3 months after delivery) followed by another longer phase (3–8 months) of hypothyroidism that, in most cases, ends up in a euthyroid situation [78] within the first year. PPT prevalence is very variable (2–20%) according to the diagnostic criteria and the methodology used for its diagnosis [79]. In general, symptoms belonging to both the thyrotoxic phase and the hypothyroid phase are minor and unspecific. Thus, many cases are not diagnosed. The symptoms include the appearance of goiter some months after delivery, emotional lability, depression, fatigue and/or palpitations. The diagnosis can be established by determining TSH and fT_4. During the thyrotoxicity phase the uptake of iodine or radioactive technetium is low, which enables us to differentiate it from puerperal Graves' disease. Treatment is not required, except in cases with intense symptoms – since the hormones released are not due to a synthesis increase but to glandular damage. In serious conditions, a brief treatment with β-blockers is required. During the hypothyroidism phase the symptoms are temporary and the consequences minimal, which means that only certain intense cases require a substitute treatment with T_4.

Thyroid hormones and fetal brain development

The organ most vulnerable to iodine and thyroid hormone deficits is the central nervous system. Iodine deficit may provoke permanent brain damage without the clinical signs of goiter being evident. The correction of a deficit has different consequences depending on the time of the treatment's administration: the correction of an iodine deficit during the second trimester reduces neurological anomalies, increases cephalic size and improves the development quotient. However, correction at later stages of pregnancy does not improve the neurological development, although it tends to produce a bigger cephalic circumference and the intelligence quotient (IQ) development is larger than in that infants whose mothers receive no iodine supplement [80].

Congenital hypothyroidism

Traditionally, research on the role of the thyroid hormones in brain development has focused on the postnatal phase and on identifying congenital hypothyroidism, which is the final result of the deficiency suffered throughout the pregnancy. Iodine deficit during pregnancy produces an increase in perinatal mortality and low birth weight which can be prevented by iodated oil injections given in the latter half of pregnancy or in other supplementary forms [81]. The epidemiological studies suggest that hypothyroxinemia, especially at the beginning of pregnancy, affects the neurological development of the new human being in the long term. Full-scale clinical studies have demonstrated a correlation between maternal thyroid insufficiency during pregnancy and a low intellectual quotient in the neonate [82,83]. However, the seriousness and irreversibility of neonatal lesions are not related to the degree of iodine deficit but rather with the period when the deficit is suffered. Maternal hypothyroxinemia during the first gestational trimester limits the possibilities of postnatal neurodevelopment [84,85]. The most serious form of brain lesion corresponds to neurological cretinism, but mild degrees of maternal hypothyroxinemia also produce alterations in psychomotor development [76,86,87].

The thyroid function of neonates at birth is significantly related to the brain size and its development during the first two years of life [88]. Screening programs for neonatal congenital hypothyroidism indicate that it is present in approximately one case out of 3000 to 4000 live births [89]. Seventy-eight percent were found to have an IQ of over 85 when congenital hypothyroidism was diagnosed within the first few months after birth, 19% when it was diagnosed between 3 and 6 months, and 0% when the diagnosis was made 7 months after birth. In a meta-analysis of seven studies [90], a decrease of 6.3 IQ points was found among neonates who suffered hypothyroidism during pregnancy in comparison to the control group. Long-term sequelae of hypothyroidism also affect intellectual development during adolescence. The affected children show an average of 8.5 IQ points less than the control group, with deficits in memory and in visuospatial and motor abilities related to the seriousness of congenital hypothyroidism and due to inadequate treatment in their early childhood [91].

Thyroid hormones during early brain development

Maternal euthyroidism is a critical factor for fetal brain development during the first 12–14 weeks of pregnancy. The fetal brain expresses the nuclear receptors for T_3 from at least the 10th gestational week and its concentration in the brain and other tissues increases up to ten times during the second gestational trimester [92]. The major effects of T_4 act on somatogenesis, neuronal differentiation and the formation of the neuronal process especially in the cerebral cortex, cochlea and basal ganglia; brain growth and its differentiation become more significant during the third trimester [80,93]. In pregnant rats, insufficient thyroid hormone alters the migration of neurons in the cerebral cortex and hippocampus resulting in the presence of neurons in abnormal brain areas of the neonate [94]. The results prove that maternal hypothyroxinemia might affect neonatal development as well as the cytoarchitecture of the nervous tissue. If we extrapolate these results to humans, they reinforce the argument that iodine deficiency during pregnancy or even before conception should be prevented with the aim of guaranteeing optimum health. It seems that the importance of an adequate iodine supplement during pregnancy leaves no place for controversy.

Human fetal tissue is exposed to significant quantities of maternal-origin T_4 [69]. During the greater part of the first trimester of pregnancy, there are two cavities surrounding the embryo: the amniotic sac that contains the embryo, and the exocelomic cavity corresponding to the secondary yolk sac which is directly connected to the fetal digestive tract and the circulatory system. The exocelomic space is where significant fetal–maternal molecular exchanges take place, and it is a reservoir of ultra-filtered fluid from the maternal serum with nutrients and trophoblast products necessary for the embryo. In the celomic fluid, the presence of T_4 has been found as early as the 6th gestational week [62]. At the end of the first trimester of pregnancy, the exocelomic cavity is progressively obliterated by the growing amniotic cavity containing the fetus, and the maternal nutrients are transferred to the fetal bloodstream via the placenta from the 12th gestational week onwards. Overcoming numerous methodological difficulties, Calvo and colleagues [69] studied the thyroid iodothyronines in the extraembryonic cavities, maternal circulation and embryonic tissue of euthyroid pregnant women. They demonstrated that the concentrations of T_4 and T_3 in the fetal compartment are 100 times lower than those present in the maternal serum; however, in all extraembryonic fluids the concentration of fT_4 is a third that of the mother's. It is thought that maternal hypothyroxinemia at the beginning of pregnancy affects the quantity of fT_4 available for the embryo to transform into the active T_3 hormone. This possibility coincides perfectly with the evidence that the fetal brain activity of D_3 is higher than in the adult brain [95]. Also, the low concentration of T_3, the high concentration of rT_3 and the high molar rT_3/T_4 ratio suggest that iodothyronines transferred from the mother to the extraembryonic fluids are

submitted to the same process of inactivation as in the most advanced phases of development [96].

T_4 turns into the active hormone T_3 in the glial cells, astrocytes and tanycytes, although the target cells are the neurons and the maturing oligodendrocytes. T_3 acts via the specific thyroid receptors that control myelinization, cellular differentiation, migration and signaling. Apart from the effects mediated by receptors, in unbounded conditions the hormone has effects on transcription repressors [97]. The main isoforms of the TRs have been identified to be present in the cerebral cortex from the 8th gestational week, as well as a positive immunostaining being found for TR expression in cerebellar pyramidal cells and Purkinje cells at this time [94,97]. The receptors appear to be occupied by thyroid hormones at different physiological levels from the 9th gestational week [98].

Iodine supplements

The main procedure used to correct iodine deficiency is universal salt iodination by adding iodide or iodate to salt, with an iodine content varying from 7 to 100 mg per kg of salt. In the European Union a common policy should be established to guarantee compulsory salt iodination, although this is a difficult matter due to the different culinary habits of the people of each member country. Another alternative would be to provide specific recommendations to avoid the problem of subclinical hypothyroidism and the low iodine levels found in a vast number of Europeans.

In the USA, diet supplementation with iodine was introduced in the first third of the 20th century to prevent the appearance of goiter. This consisted of adding 100 mg of potassium iodate per kilogram of edible salt, which corresponds to a daily intake of approximately 0.5 mg. Salt was selected as the medium for iodine supplementation because its intake is uniform across all socioeconomic strata and throughout all seasons of the year. Supplementation is achieved using simple technology, and the program is inexpensive. In other countries lower doses are used to guarantee the prevention of cretinism and goiter. For instance, in Switzerland, 15 mg/kg salt is used [99]. Another recommended alternative is the administration of a massive annual dose of slow-release iodinated oil.

The Norwegian population has been considered iodine-replete for decades with an iodine intake above the Recommended Dietary Allowance of 150 μg. Iodine intake has been studied in nationwide dietary studies among children and adults. In adults, the average iodine intake is 136 μg/day in women and 175 μg/day in men. Fifty-five percent of this intake derives from milk, 20% from fish, and the iodine contribution from drinking water is negligible [100]. In Finland, it appears that the iodine intake has reached appropriate levels. Thus, actions aimed at intensifying iodine prophylaxis are not being considered. For the last 20 years the intake has been considered adequate, it is four to five greater than in the mid-1950s, when endemic goiter was common. In spite of the controlled deficiency situation, some seasonal variations have been found in terms of the ingested quantity in summer vs. winter [101].

In Germany, the iodine quantity ingested by humans and animals has increased as shown by studying the iodine content of human milk and cow's milk. Iodized salt was introduced in Germany in the early 1980s. A nationwide study showed that iodine levels among the population have improved since the introduction of the supplementation. Buhling and associates [102] studied the goiter volume in pregnant German women by ultrasound and collected serum and urine samples; 58% were taking iodine supplements. The average iodine/creatinine ratio was 181 μg/g and 20.4% of the women had a ratio of between 50 and 100 μg/g, which corresponds to WHO grade I iodine deficiency. The patients taking iodine supplements had significantly higher iodine/creatinine ratio and slightly lower serum TG levels than non-supplemented patients. The prevalence of increased thyroid size indicates a prolonged iodine deficit, while 20.4% of pregnant women suffer from an iodine deficit which may be corrected with an adequate supplement. In Spain, almost half of pregnant women had iodine deficit; in 2004 the Spanish Congress made recommendations to the regional authorities to counteract the problems related to iodine deficiency, particularly those suffered during pregnancy and breastfeeding [103]. Unfortunately, iodine deficiency is still a public health problem in Spain [104,105].

Different international bodies such as WHO, UNICEF, ICCIDD and the European Commission recommend a daily intake of 150 μg of iodine in non-pregnant adults [5,76]. This quantity was established based on studies on iodine accumulation and turnover, the necessary amount required to maintain euthyroidism in athyreotics, the normal levels of T_4, and the iodine dose necessary to prevent the appearance of goiter in the general population. The American Thyroid Association recommends that women should receive 150 μg iodine supplements daily during pregnancy and lactation [106].

Many consumers prefer natural products to improve their dietary content of micronutrients instead of artificial compounds such as iodinated salt. Seaweed is eaten in many countries, especially in Japan, and it is making its way into the Western diet due to its nutritive and medicinal properties. Nevertheless, the composition of seaweed varies depending on the species and origin and it may even be contaminated by heavy metals (mercury, lead) and

radioactive isotopes. The seaweed *Laminaria japonica* is rich in iodine content followed by the common seaweed in the Western coast of Canada, *Laminaria setchellii* [107]. The seaweeds *Laminaria hyperborea* and *Gracilaria verrucosa* have high iodine content as a mineral or an organic form, and have low levels in heavy metals [108]. The use of *G. verrucosa* is more effective than the use of *L. hyperborea* to increase the bioavailable iodine in normal individuals with sufficient iodine levels or with mild iodine deficiency.

It is estimated that the daily intake of 200 μg of iodine prevents the appearance of goiter related to pregnancy [109]. The US Institute of Medicine of the National Academy of Sciences has determined an Estimated Average Requirement (EAR) for a particular nutrient as the quantity which would be enough for 50% of the population, the recommended daily intake is then calculated from this value; for iodine the EAR value is 160 μg/day and the recommended daily dose is 220 μg/day [75].

Iodine supplements during pregnancy are considered secure, though there is the possibility that a high iodine dose might suppress maternal thyroid function. Mahomed and Gulmezoglu [110], on behalf of the Cochrane Foundation, assessed the effects of iodine supplementation before and during pregnancy in iodine-deficient areas. For this purpose, three trials provided clinical outcomes; in two trials, the iodine supplements were accompanied by a significant reduction in the infant mortality rate. The iodine supplements also reduced the prevalence of endemic cretinism at the age of 4 years, and better psychomotor development was obtained between 4 and 25 months of age. Moreover, the benefits achieved were not accompanied by any obvious side-effects.

In Germany, Bader and collaborators [111] studied the iodine content in milk of lactating women five days after delivery and in bulk samples of cow's milk to determine if the iodine increase in milk was one of the reasons for an improved iodine supply. The average iodine content of human milk was 169 μg/l and in cow's milk 178 μg/l. The iodine quantity in maternal milk was twice as high as the levels in mothers in 1994 in the same area. In some countries, based on limited available data, iodine levels in breast milk may be significantly lower than they were two decades ago due to the presence of perchlorate and other contaminants. Therefore, the recommended iodine intake for pregnant and lactating women may need to be revised and increased [17].

Risks of an excess of iodine

The generalized supply of iodine has been the cause of criticism and alarm. The first studies that were carried out on iodine supplementation were accompanied by an increase in hyperthyroidism cases which began with weight loss, weakness, signs of heart failure and nervousness, often with no increase in the size of the thyroid gland or of the exophthalmos [112]. This effect occurs almost exclusively in people over the age of 50, thus it does not occur in people who are at a reproductive age. It appears that this problem affects the initial iodination in large populations and the prolonged deficit suffered by people of a certain age, but this should not be an obstacle for the overall eradication of the problem in a specific community.

The normal thyroid gland adapts to the moderate load of iodine through self-regulation. Numerous studies have proved that iodine supplementation in an iodine-deficient population causes an increase in the number of diagnosed cases of hyperthyroidism [113]. The effects of edible salt supplementation and the appearance of hyperthyroidism 6 years later have been especially high among people between aged 20–39 years, and new cases are alleged to be of an autoimmune nature [115]. Teng and co-workers [115] studied China's iodine supplementation, and its effects over time on the iodine levels and ultrasound characteristics of the thyroid gland in both 'mildly deficient' populations and populations with 'more-than-adequate' or 'excessive' levels of iodine intake. They found that increased iodine intake over time is linked to decreased thyroid function, and they concluded that though iodine supplements should be implemented to prevent and treat iodine-deficiency disorders, excessive levels of iodine do not appear to be safe. In the editorial that accompanies the Chinese work, Utiger [116] points out: 'Levels that are more than adequate . . . or excessive . . . do not appear to be safe.'

Final remarks

Adverse obstetric and neonatal outcomes have been demonstrated in pregnant women who do not receive sufficient quantities of iodine during pregnancy and lactation. One of the consequences of maternal iodine deficiency is subclinical hypothyrodism. This causes alterations in the mechanisms of trophoblastic implantation, in the transport of hormones and in early embryonic development, when the iodinated hormones from the mother play a crucial role in early embryonic organogenesis, particularly related to the central nervous system. Before fetal hormonal synthesis starts, the transplacental passage of thyroid hormones plays an essential part in fetal development. Thyroid hormone receptors and iodothyronine deiodinases are present in the placenta and in the fetal central nervous tissue. The accumulated evidence available suggests that both the professionals in charge of assisting pregnant women and the affected women should be informed that a suitable quantity of iodine can improve perinatal outcome. This can be

achieved with a diet based on products which are rich in iodine and, if necessary, with a supplement. A global health effort is required to obtain optimum conditions at birth. The problem is universal and affects both rich and poor.

References

1. Moghissi KS. Risks and benefits of nutritional supplements during pregnancy. Obstet Gynecol 1981;58(Suppl): 68S–78S.
2. Dobson JE. The iodine factor in health and evolution. Geographical Rev 1998;88:1–14.
3. Correia HR, Balseiro SC, de Areia ML. Are genes of human intelligence related to the metabolism of thyroid and steroids hormones? – endocrine changes may explain human evolution and higher intelligence. Med Hypotheses 2005;65:1016–1023.
4. Richardson SJ, Monk JA, Shepherdley CA, Ebbesson LOE, Sin F, Power DM, Frappell PB, Köhrle J, Renfree MB. Developmentally regulated thyroid hormone distributor proteins in marsupials, a reptile, and fish. Am J Physiol Regul Integr Comp Physiol 2005;288:R1264–R1272.
5. European Commission, Health & Consumer Protection Directorate-General. Opinion of the Scientific Committee on Food on the tolerable upper intake level of iodine. SCF/CS/NUT/UPPLEV/26 Final. Brussels: European Union, Oct 7 2002. pp 1–25.
6. United Nations. World declaration on the survival, protection and development of children and a plan of action for implementing the development of children in the 1990s. New York: United Nations, 1990.
7. Amachi S, Kasahara M, Hanada S, Kamagata Y, Shinoyama H, Fujii T, Muramatsu Y. Microbial participation in iodine volatilization from soils. Environ Sci Technol 2003;37:3885–3890.
8. Dai JL, Zhu YG, Zhang M, Huang YZ. Selecting iodine-enriched vegetables and the residual effect of iodate application to soil. Biol Trace Elem Res 2004;101: 265–276.
9. De Groef B, Decallonne BR, Van der Geyten S, Darras VM, Bouillon R. Perchlorate versus other environmental sodium/iodide symporter inhibitors: potential thyroid-related health effects. Eur J Endocrinol 2006;155:17–25.
10. Skjoldebrand L, Brundin J, Carlstrom A, Pettersson T. Thyroid associated components in serum during normal pregnancy. Acta Endocrinol 1982;100:504–511.
11. Hennemann G, Docter R, Friesema ECH, de Jong M, Krenning EP, Visser TJ. Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev 2001;22:451–476.
12. Friesema EC, Ganguly S, Abdalla A, Manning Fox JE, Halestrap AP, Visser TJ. Identification of monocarboxylate transporter 8 as a specific thyroid hormone transporter. J Biol Chem 2003;278:40128–40135.
13. Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M, Barrett TG, Mancilla EE, Svensson J, Kester MH, et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. Lancet 2004;364:1435–1437.
14. Dumitrescu AM, Liao XH, Best TB, Brockmann K, Refetoff S. A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. Am J Hum Genet 2004;74:168–175.
15. Sánchez CA, Crump KS, Krieger RI, Khandaker NR, Gibbs JP. Perchlorate and nitrate in leafy vegetables of North America. Environ Sci Technol 2005;39:9391–9397.
16. Dyke JV, Ito K, Obitsu T, Hisamatsu Y, Dasgupta PK, Blount BC. Perchlorate in dairy milk. Comparison of Japan versus the United States. Environ Sci Technol 2007;41: 88–92.
17. Kirk AB, Martinelango PK, Tian K, Dutta A, Smith EE, Das Dupta PK. Perchlorate and iodide in dairy and breast milk. Environ Sci Technol 2005;39:2011–2017.
18. van Maanen JM, van Dijk A, Mulder K, de Baets MH, Menheere PC, van der Heide D, Mertens PL, Kleinjans DC. Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid. Toxicol Lett 1994;72: 365–374.
19. Dorea JG. Maternal thiocyanate and thyroid status during breast-feeding. J Am Coll Nutr 2004;23:97–101.
20. Laurberg P, Nohr S, Pedersen K, Fuglsang E. Iodine nutrition in breast-fed infants is impaired by maternal smoking. J Clin Endocrinol Metab 2004;89:181–187.
21. Ribas-Fito N, Sala M, Cardo E, Mazon C, De Muga ME, Verdu A, Marco A, Grimalt JD, Sunyer J. Organochlorine compounds and concentrations of thyroid stimulating hormone in newborns. Occupat Environ Med 2003;60: 301–303.
22. Foster WG, Holloway AC, Hughes CL Jr. Dioxin-like activity and maternal thyroid hormone levels in second trimester maternal serum. Am J Obstet Gynecol 2005;193: 1900–1907.
23. Wang SL, Su PH, Jong SB, Guo YL, Chou WL, Papke O. *In utero* exposure to dioxins and polychlorinated biphenyls and its relations to thyroid function and growth hormone in newborns. Environ Sci Technol 2005;113:1645–1650.
24. Takser L, Mergler D, Baldwin M, de Grosbois S, Smargiassi A, Lafond J. Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. Environ Sci Technol 2005;113:1039–1045.
25. Toldy E, Locsei Z, Rigo E, Kneffel P, Szabolcs I, Kovacs GL. Comparative analytical evaluation of thyroid hormone levels in pregnancy and in women taking oral contraceptives: a study from an iodine deficient area. Gynecol Endocrinol 2004;18:219–226.
26. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev 2001;81:1097–1142.
27. Muñoz A, Bernal J. Biological activities of thyroid hormone receptors. Eur J Endocrinol 1997;137:433–445.
28. Peeters RP, van der Deure WM, Visser J. Genetic variation in thyroid hormone pathway genes; polymorphisms in the TSH receptor and the iodothyronine deiodinases. Eur J Endocrinol 2006;155:655–662.
29. Hansen PS, Brix TH, Sorensen TI, Kyvik KO, Hegedus L. Major genetic influence on the regulation of the pituitary–thyroid axis: a study of healthy Danish twins. J Clin Endocrinol Metab 2004;89:1181–1187.
30. Samollow PB, Perez G, Kammerer CM, Finegold D, Zwartjes PW, Havill LM, Comuzzie AG, Mahaney MC, Goring HH, Blangero J, et al. Genetic and environmental influences on thyroid hormone variation in Mexican Americans. J Clin Endocrinol Metab 2004;89:3276–3284.
31. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L, Jorgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 2005;90: 4019–4024.
32. Poppe K, Velkeniers B. Thyroid disorders in infertile women. Ann Endocrinol (Paris) 2003;64:45–50.
33. Sieiro Netto L, Medina Coeli C, Micmacher E, Mamede Da Costa S, Nazar L, Galvao D, Buescu A, Vaisman M. Influence of thyroid autoimmunity and maternal age on the risk of miscarriage. Am J Reprod Immunol 2004;52:312–316.

34. Bussen S, Steck T, Dietl J. Increased prevalence of thyroid antibodies in euthyroid women with a history of recurrent *in-vitro* fertilization failure. Hum Reprod 2000;15:545–554.
35. la Marca A, Morgante G, De Leo V. Human chorionic gonadotropin, thyroid function, and immunological indices in threatened abortion. Obstet Gynecol 1998;92:206–211.
36. Bischof P, Meisser A, Campana A. Paracrine and autocrine regulators of trophoblast invasion – a review. Placenta 2000; 21(Suppl A):S55–S60.
37. Craven CM, Zhao L, Ward K. Lateral placental growth occurs by trophoblast cell invasion of decidual veins. Placenta 2000;21:160–169.
38. Matsuo H, Maruo T, Murata K, Mochizuki M. Human early placental trophoblasts produce an epidermal growth factor-like substance in synergy with thyroid hormone. Acta Endocrinol 1993;128:225–229.
39. McKinnon B, Li H, Richard K, Mortimer R. Synthesis of thyroid hormone binding proteins transthyretin and albumin by human trophoblast. J Clin Endocrinol Metab 2005;90: 6714–6720.
40. Kilby MD, Verhaeg J, Gittoes N, Somerset DA, Clark PM, Franklyn JA. Circulating thyroid hormone concentrations and placental thyroid hormone receptor expression in normal human pregnancy and pregnancy complicated by intrauterine growth restriction (IUGR). J Clin Endocrinol Metab 1998; 83:2964–2971.
41. Chan S-Y, Franklyn JA, Pemberton HN, Bulmer JN, Visser TJ, McCabe CJ, Kilby MD. Monocarboxylate transporter 8 expression in the human placenta: the effects of severe intrauterine growth restriction. J Endocrinol 2006;189:465–471.
42. Di Cosmo C, Fanelli G, Tonacchera M, Ferrarini E, Dimida A, Agretti P, De Marco G, Vitti P, Pinchera A, Bevilacqua G, et al. The sodium–iodide symporter expression in placental tissue at different gestational age: an immunohistochemical study. Clin Endocrinol (Oxf) 2006;65:544–548.
43. Bidart JM, Lacroix L, Evain-Brion D, Caillou B, Lazar V, Frydman R, Bellet D, Filetti S, Schlumberger M. Expression of Na^+/I^- symporter and Pendred syndrome genes in trophoblast cells. J Clin Endocrinol Metab 2000;85:4367–4372.
44. Pérez-López FR, Abós MD, González Moreno CM, Corvo RH, Andonegui JA. Lack of effect of maternal administration of clebopride on fetal prolactin and thyrotropin serum levels. Neuroendocrinol Lett 1982;4:283–287.
45. Pérez-López FR, Robert J, Teijeiro J. PRL, TSH, β-hCG and oestriol responses to repetitive (triple) LRH/TRH administration in the third trimester of human pregnancy. Acta Endocrinol 1984;106:400–404.
46. Pérez-López FR, Aisa F, Urcia M, Martínez-Casamayor MF, Farjas MP. Circadian oscillations of thyrotrophin, prolactin, cortisol, placental lactogen and estriol in late human pregnancy. Neuroendocrinol Lett 1984;6:231–241.
47. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? J Clin Endocrinol Metab 2007;92:203–207.
48. Glinoer D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (hCG) and its free α and β subunits, in relation to maternal thyroid stimulation during normal pregnancy. J Endocrinol Invest 1993;16:881–888.
49. Glinoer D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejeune B. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 1990;71:276–287.
50. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404–433.
51. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65: 689–696.
52. Roti E, Gardini E, Minelli R, Bianconi L, Flisi M. Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. J Endocrinol Invest 1991;14:1–9.
53. Ball R, Freedman DB, Holmes JC, Midgley JEM, Sheehan CP. Low-normal concentrations of free thyroxin in serum in late pregnancy: physiological fact, not detected artifact. Clin Chem 1989;35:1891–1896.
54. Burrow GN. Thyroid function and hyperfunction during gestation. Endocr Rev 1993;14:194–202.
55. Vermiglio F, Lo Presti VP, Castagna MG, Violi MA, Moleti M, Finocchiaro MD, Mattina F, Artemisia A, Trimarchi F. Increased risk of maternal thyroid failure with pregnancy progression in an iodine deficient area with major iodine deficiency disorders. Thyroid 1999;9:19–24.
56. Goodwin TM, Hershman JM. Hyperthyroidism due to inappropriate production of human chorionic gonadotropin. Clin Obstet Gynecol 1997;40:32–44.
57. Kennedy RL, Darne J. The role of hCG in regulation of the thyroid gland in normal and abnormal pregnancy. Obstet Gynecol 1991;78:298–307.
58. Utiger RD. Maternal hypothyroidism and fetal development. N Engl J Med 1999;341:601–602.
59. Foulk RA, Musci TJ, Schriock ED, Taylor RN. Does human chorionic gonadotropin have human thyrotropic activity *in vivo*? Gynecol Endocrinol 1997;11:195–201.
60. Eltom A, Eltom M, Elnagar B, Elbagir M, Gebre-Medhin M. Changes in iodine metabolism during late pregnancy and lactation: a longitudinal study among Sudanese women. Eur J Clin Nutr 2000;54:429–433.
61. Eltom A, Eltom M, Idris M, Gebre-Medhin M. Thyroid function in the newborn in relation to maternal thyroid status during labour in a mild iodine deficiency endemic area in Sudan. Clin Endocrinol (Oxf) 2001;55:485–490.
62. Contempré B, Jauniaux E, Calvo R, Jurkovic D, Campbell S, Morreale de Escobar G. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. J Clin Endocrinol Metab 1993;77:1719–1722.
63. Vulsma T, Gons MH, de Vijlder JJ. Maternal–fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. N Engl J Med 1989;321:13–16.
64. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. N Engl J Med 1991;324:532–536.
65. Ballard PL, Ballard RA, Ning Y, Cnann A, Boardman C, Pinto-Martin J, Polk D, Phibbs RH, Davis DJ, Mannino FL, et al. Plasma thyroid hormones in premature infants: effect of gestational age and antenatal thyrotropin releasing hormone treatment. Pediatr Res 1998;44:642–649.
66. Nohr SB, Laurber P. Opposite variations in maternal and neonatal thyroid function induced by iodine supplementation during pregnancy. J Clin Endocrinol Metab 2000;85:623–627.
67. Radaelli T, Cetin I, Zamperini P, Ferrazzi E, Pardi G. Intrauterine growth of normal thyroid. Gynecol Endocrinol 2002;16:427–430.
68. Hume R, Simpson J, Delahunty C, van Toor H, Wu SY, Williams FLR, Visser TJ; with collaboration from the Scottish Preterm Thyroid Group. Human fetal and cord serum thyroid hormones: developmental trends and interrelationships. J Clin Endocrinol Metab 2004;89:4097–4103.

69. Calvo RM, Jauniaux E, Gulbis B, Asuncion M, Gervy C, Contempre B, Morreale de Escobar G. Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. J Clin Endocrinol Metab 2002;87:1768–1777.
70. Kester MHA, de Mena RM, Obregón MJ, Marinkovic D, Howatson A, Visser TJ, Hume R, Morreale de Escobar GM. Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. J Clin Endocrinol Metab 2004;89:3117–3128.
71. Ballibio M, Nicolini U, Jowett T, Ruiz de Elvira MC, Ekins RP, Rodeck CH. Maturation of thyroid function in normal human foetuses. Clin Endocrinol (Oxf) 1989;31:565–571.
72. Koopdonk-Kool JM, De Vijlder JJM, Veenboer GJM, Ris-Stalpers C, Kok JH, Vulsma T, Boer K, Visser TJ. Type II and type III deiodinase activity in human placenta as function of gestational age. J Clin Endocrinol Metab 1996;81:2154–2158.
73. Kohrle J. Thyroid hormone deiodinases – a selenoenzyme family acting as gate keepers to thyroid hormone action. Acta Med Austr 1996;23:17–30.
74. Chan SS, Hams G, Wiley V, Wilcken B, McElduff A. Postpartum maternal iodine status and the relationship to neonatal thyroid function. Thyroid 2003;13:873–876.
75. Institute of Medicine, Food and Nutrition Board. Iodine. In: Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington (DC): National Academy Press; 2001. pp 258–289.
76. World Health Organization/United Nations Children's Fund/International Council for the Control of Iodine Deficiency Disorders. Assessment of the iodine deficiency disorders and monitoring their elimination. WHO/NHD/01.1. Geneva: WHO; 2001. pp 1–107.
77. Ares S, Quero J, Duran S, Presas MJ, Herruzo R, Morreale de Escobar G. Iodine content of infant formulas and iodine intake of premature babies: high risk of iodine deficiency. Arch Dis Child Fetal Neonatal Ed 1994;71:F184–F191.
78. Terry AJ, Hague WM. Postpartum thyroiditis. Semin Perinatol 1998;22:497–502.
79. Gerstein HC. How common is postpartum thyroiditis? Arch Inter Med 1990;150:1397–1400.
80. DeLong GR, Xue-Yi C, Xin-Min J. Iodine supplementation of a cross-section of iodine-deficient pregnant women: does the human fetal brain undergo metamorphosis? In: Stanbury JB, Delange F, Dunn JT, Pandav CS, editors. Iodine in pregnancy. Delhi: Oxford University Press; 1998. pp 55–78.
81. World Health Organization. The WHO global database on iodine deficiency [Internet]. Geneva: WHO; c2004 [cited Nov 2 2006]. Available from: http://whqlibdoc.who.int/publications/2004/9241592001.pdf
82. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549–555.
83. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 1999;50:149–155.
84. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 2003;59:282–288.
85. Kooistra L, Crawford S, van Baar AL, Brouwers EP, Pop VJ. Neonatal effects of maternal hypothyroxinemia during early pregnancy. Pediatrics 2006;117:161–167.
86. Morreale de Escobar G, Obregón MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. Eur J Endocrinol 2004;151(Suppl 3):U25–U37.
87. Visser TJ. The elemental importance of sufficient iodine intake: a trace is not enough. Endocrinology 2006;147:2095–2097.
88. Van Vliet G. Neonatal hypothyroidism: treatment and outcome. Thyroid 1999;9:79–84.
89. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML. Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 1991;35:41–46.
90. Derksen-Lubsen G, Verkerk PH. Neuropsychologic development in early treated congenital hypothyroidism: analysis of literature data. Pediatric Res 1996;39:561–566.
91. Rovet JF. Congenital hypothyroidism: long-term outcome. Thyroid 1999;9:741–748.
92. Bernal J, Pekonen F. Ontogenesis of the nuclear 3,5,3′-triiodothyronine receptor in the human fetal brain. Endocrinology 1984;114:677–679.
93. Chan S, Kilby MD. Thyroid hormone and central nervous system development. J Endocrinol 2000;165:1–8.
94. Lavado-Autric R, Auso E, Garcia-Velasco JV, Arufe MC, Escobar del Rey F, Berbel P, Morreale de Escobar G. Early maternal hypothyroxinemia alters histogenesis and cerebral cortex cytoarchitecture of the progeny. J Clin Invest 2003;111:1073–1082.
95. Santini F, Pinchera A, Ceccarini G, Castagna M, Rosellini V, Mammoli C, Montanelli L, Zucchi V, Chopra IJ, Chiovato L. Evidence for a role of the type III-iodothyronine deiodinase in the regulation of 3,5,3′-triiodothyronine content in the human central nervous system. Eur J Endocrinol 2001;144:577–583.
96. Huang SA, Dorfman DM, Genest DR, Salvatore D, Larsen PR. Type 3 iodothyronine deiodinase is highly expressed in the human uteroplacental unit and in fetal epithelium. J Clin Endocrinol Metab 2003;88:1384–1388.
97. Bernal J. Thyroid hormones and brain development. Vitam Horm 2005;71:95–122.
98. Kilby MD, Gittoes N, McCabe C, Verhaeg J, Franklyn JA. Expression of thyroid receptor isoforms in the human fetal central nervous system and the effects of intrauterine growth restriction. Clin Endocrinol (Oxf) 2000;53:469–477.
99. Bürgi H, Supersaxo Z, Selz B. Iodine deficiency disease in Switzerland one hundred years after Theodor Kocher's survey: a historical review with some new goitre prevalence data. Acta Endocrinol 1990;13:577–590.
100. Dahl L, Johansson L, Julshamn K, Meltzer HM. The iodine content of Norwegian foods and diets. Public Health Nutr 2004;7:569–576.
101. Varo P, Saari E, Paaso A, Koivistoinen P. Iodine in Finnish foods. Int J Vitam Nutr Res 1982;52:80–89.
102. Buhling KJ, Schaff J, Bertram H, Hansen R, Muller C, Wascher C, Heinze T, Dudenhausen JW. [Supply of iodine during pregnancy – an inventory in Berlin, Germany]. Zeitschrift Geburtsh Neonatol 2003;207:12–16.
103. Ministerio de Sanidad y Consumo. Prevención de la deficiencia de yodo durante el embarazo y la lactancia [Internet]. Madrid: Ministerio de Sanidad y Consumo; undated [cited Jan 3 2007]. Available from: http://www.msc.es/profesionales/saludPublica/prevPromocion/docs/yodoEmbarazo.pdf
104. Foz M. La deficiencia de yodo en España: un problema todavía no resuelto. Med Clín (Barc) 2004;122:459–460.
105. Pérez-López FR. Prescribir yodo durante el embarazo. Siete Días Médicos 2006;684:60.
106. Becker DV, Braverman LE, Delange F, Dunn JT, Franklyn JA, Hollowell JG, Lamm SH, Mitchell ML, Pearce E, Robbins J, et al. Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. Thyroid 2006;16:949–951.

107. van Netten C, Hoption Cann SA, Morley DR, van Netten JP. Elemental and radioactive analysis of commercially available seaweed. Sci Total Environ 2000;255:169–175.
108. Aquaron R, Delange F, Marchal P, Lognone V, Ninane L. Bioavailability of seaweed iodine in human beings. Cell Mol Biol 2002;48:563–569.
109. DeLong GR, Leslie PW, Wang S-H, Jiang XM, Zhang ML, Rakerman M, Jiang JY, Ma T, Cao XY. Effect on infant mortality of iodination of irrigation water in a severely iodine-deficient area of China. Lancet 1997;350:771–773.
110. Mahomed K, Gulmezoglu AM. Maternal iodine supplements in areas of deficiency. Cochrane Database Syst Rev 2000;(2):CD000135.
111. Bader N, Moller U, Leiterer M, Franke K, Jahreis G. Pilot study: tendency of increasing iodine content in human milk and cow's milk. Exp Clin Endocrinol Diabetes 2005;113: 8–12.
112. Kohn LA. The midwestern American 'epidemic' of iodine-induced hyperthyroidism in the 1920s. Bull N Y Acad Med 1976;52:770–781.
113. Galofré JC, Fernández-Calvet L, Ríos M, García-Mayor RV. Increased incidence of thyrotoxicosis after iodine supplementation in an iodine sufficient area. J Endocrinol Invest 1994;17:23–27.
114. Pedersen IB, Laurberg P, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Rasmussen LB. Increase in incidence of hyperthyroidism predominantly occurs in young people after iodine fortification of salt in Denmark. J Clin Endocrinol Metab 2006;91:3830–3834.
115. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, et al. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006;354:2783–2793.
116. Utiger RD. Iodine nutrition – more is better . . . N Engl J Med 2006;354:2819–2821.