

IODINE DEFICIENCY DISORDERS

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I-INTRODUCTION

The four most important deficiency diseases in developing countries today are protein-energy malnutrition (PEM), xerophthalmia, nutritional anemia, and iodine deficiency disorders.

Control of these nutritional diseases requires systematic diagnosis of the existing situation and appropriate intervention strategies such as targeted food and specific micronutrient supplementation, food fortification, nutrition education, and reductions in infections as well as general improvements in economic conditions and social equity.

Iodine deficiency is the leading cause of preventable intellectual impairment and is associated with a spectrum of neurological and developmental pathology. More than one billion people are at risk. The technology of iodine deficiency intervention is well established. Iodized salt, the preferred method, is easy to produce, administer in physiologic doses, and is cost effective.

1-IODINE DEFICIENCY DISORDERS

The adoption of the term Iodine Deficiency Disorders reflects a new dimension of understanding of the full spectrum of the effects of iodine deficiency on the fetus, the neonate, the child and adolescent, and the adult in an entire population.

Any national effort to eliminate iodine deficiency must extend far beyond the Ministry of Health. The program will require the full participation of a range of national agencies and the full support and participation of HEALTH and other related professionals.

2-IODINE METABOLISM NEEDS AND RELATED NUTRITIONAL ASPECTS- THE ECOLOGY OF IODINE DEFICIENCY

The human organism depends on exogenic supply of iodine. The deficiency leads to an endemic goiter. The causes are among others as follows: Small geochemical offer of iodine with low iodine content of vegetable and animal products and of drinking water as well as moderate consume of fish.

There is a cycle of iodine in nature, and most iodine exists in the ocean. It was present (by glaciations, snow, rain) in primordial surface soil and was carried by the wind, rivers, and floods into the sea. The most likely areas to be leached are the mountainous areas of the world; it occurs also, however, in flooded river valleys.

Iodine occurs in soil and in the sea as iodide. Iodide ions are oxidized by sunlight to elemental iodine (which is volatile), so that every year some 400,000 tons of iodine escapes from the surface of the sea. The concentration of iodide in sea water is about 50 micrograms/L; in the air it is approximately 0.7 micrograms/cubic meter. Iodine in the atmosphere is returned to the soil by rain, which has concentrations in the range of 1.8 to 8.5 micrograms/L. In this way, the cycle is completed. The return of iodine, however, is slow and small in amount compared with the original loss, and subsequent repeated flooding ensures that iodine deficiency in the soil continues. There is no natural correction, and iodine deficiency will persist in soil indefinitely. All crops grown in this soil will be iodine deficient. As a result, human and animal populations, which are totally dependent on food grown in such soil, become iodine deficient. This accounts for the occurrence of severe iodine deficiency in vast populations in Asia that live within systems of subsistence agriculture in flooded river valleys. Iodine deficiency in affected populations will continue unless there is a supplement provided or, alternatively, diversification of the diet occurs with an increase in iodine intake derived from food sources outside the iodine-deficient areas.

3-RECOMMENDED DIETARY ALLOWANCE OF IODINE

The recommended dietary allowances of iodine are:

-100 micrograms/day for adults and adolescents,

-60-100 micrograms/day for children aged 1 to 10 years,

-35-40 micrograms/day in infants aged less than 1 year.

II-IODINE DEFICIENCY CONSEQUENCES

The mechanism by which the thyroid gland adapts to an insufficient iodine supply is to **increase the trapping of iodide as well as the subsequent steps of the intra-thyroidal metabolism of iodine leading to preferential synthesis and secretion of triiodothyronine (T3)**. They are triggered and maintained by increased secretion of TSH, which is ultimately responsible for the development of goiter. The acceleration of the main steps of iodine kinetics and the degree of hyperstimulation by TSH are much more marked in the pediatric age groups, including neonates, than in adults, and the development of goiter appears as an unfavorable side effect in the process of adaptation to iodine deficiency during growth.

An insufficient dietary supply of iodine results in the development of a variety of disorders of thyroid function and development of the fetus and young infants, grouped under the general heading of Iodine Deficiency Disorders, IDD. Endemic goiter constitutes the most spectacular disorder from the clinical and epidemiological point of view. However, **the most serious consequence of iodine deficiency is the impact on neuro-intellectual development at a population level**, varying from endemic mental retardation to the complete picture of endemic cretinism.

Considering that **mental retardation due to iodine deficiency represents the long-term consequence of hypothyroidism occurring during the perinatal period**, it is presently recognized that the **target** groups to the effects of iodine deficiency at a population level are, by order of priority, **the fetus, the newborn, the pregnant woman, the child** and, finally, the adult.

The newborn is more susceptible than the adult to the effects of iodine deficiency. Consequently, **systematic screening for congenital hypothyroidism in endemic areas is a particularly sensitive index for detecting the presence and action of goitrogens in the environment and for monitoring the effects of programs of iodine prophylaxis.**

Special attention should be devoted to the protection of mother and child. Within this framework, the iodine content of formula milk should be considered.

1-GOITER

Goiter defines **any enlargement of the thyroid independent of its cause.** Worldwide iodine deficiency is the single most common cause of a goiter. **Endemic goiter** occurs when the prevalence of thyroid enlargement in the population of an area exceeds 10%. Iodine deficiency superimposed on other goitrogenic factors normally present is responsible for **sporadic goiter.** However, before iodine deficiency is established, **other thyroid diseases need to be ruled out.** Very rarely increased production of TSH (secondary hyperthyroidism) or of hormones with TSH activity (e.g. HCG producing tumors), inborn errors of iodine metabolism, and defects of the thyroid hormone receptor (thyroid hormone resistance) are the cause of a goiter. Furthermore, malignancy of the thyroid and autoimmune disease (e.g. Grave's disease) may lead to a thyroid enlargement. Still, worldwide more than 90% of patients with goiter suffer from iodine deficiency.

2-PHYSIOPATHOLOGY OF GOITER

The classical concept on the mechanism of iodine deficiency induced goiter is based on decreased thyroid hormone synthesis in the presence of **iodine depletion**, which leads to **increased production of TSH**, stimulating thyroidal growth. Recent in vitro findings using thyroid cell cultures expand this concept by demonstrating that TSH regulates the differentiation and function of thyroid cells and may induce **hyperplasia**, but not cell proliferation. In contrast to TSH, the locally produced growth factors **IGF I (insulin-like growth factor I) and EGF (epidermal growth**

factor) stimulate thyroid cell proliferation. Intra-thyroidal iodine antagonizes the effects of IGF I and EGF and simultaneously stimulates transforming growth factor beta (TGF-beta), which inhibits thyroid cell proliferation. Thus, **intra-thyroidal iodine appears to regulate thyroidal growth by controlling proliferation stimulating (IGF I, EGF) and proliferation inhibiting (TGF-beta) growth factors.** Though these new insights fill several gaps of the classical concept on the pathogenesis of endemic goiter, open questions remain.

3-ENDEMIC CRETINISM

The clinical picture of endemic cretinism results from the product of two pathophysiological events. Both events share a common feature, namely iodine deficiency, but act at different points in time.

1-The first event occurs in all cretins and represents the **prenatal action of thyroid hormone deficiency on brain development**, transmitted vertically from mother to fetus, resulting in the neurological disorder of endemic cretinism.

2-The second event represents the **postnatal action of thyroid hormone deficiency on somatic as well as brain development.**

Endemic cretins with predominant neurological features have had only transient hypothyroidism in the postnatal period, evidenced by their near normal thyroid function and by a lack of hypothyroid clinical features.

By contrast, **cretins with marked myxedematous features were characterized by permanent and severe postnatal thyroid hormone deficiency.** These cretins, in addition to signs of neurological damage, were typically dwarfed, sexually immature, with marked clinical features of myxedema. This second event, influenced by the thyroid gland's morphologic response to its environment (goiter or thyroid atrophy), dictates the final clinical outcome.

In conclusion, the clinical expression of endemic cretinism is

determined by the sum of two pathophysiological processes. The first process is fetal hypothyroidism which results in the neurological damage of the disorder and the second process is the duration and magnitude of postnatal hypothyroidism which dictates the final clinical appearance.

III-GOITOGENES AND SOME OTHER NUTRITIONAL FACTORS

In most cases, deficiency syndromes occur as a result of the interaction of environmental, social and economic factors which affect food availability, requirements and utilization.

Disorders caused by iodine deficiency continue to be a major health problem in many underdeveloped areas of the world. Although dietary iodine deficiency is clearly the major etiological factor in both endemic goiter and cretinism, cofactors such as goitrogens, other trace element deficiencies and immunological mechanisms may greatly modify the expression of these disorders.

GOITROGENIC FACTORS

Severe goiter, cretinism, and the other iodine deficiency disorders (IDD) have their main cause in the lack of availability of iodine from the soil linked to a severe limitation of food exchanges.

Apart from the degrees of severity of the iodine deficiency, the frequencies and symptomatologies of cretinism and the other IDD are influenced by other goitrogenic factors and trace elements.

Other environmental goitrogenic factors might modify the adaptation of the thyroid gland and promoted the occurrence of goiter.

1-WATER CHARACTERS

The carbonate (CO₃⁻) content of drinking water supply was found to bear a significant positive correlation with the goiter rate. The calcium (Ca⁺⁺) and magnesium (Mg⁺⁺) levels of the drinking water also exhibited relatively good linear direct correlations with the percentage goiter distribution in part of the Continental Africa.(1)

In Western Colombia (2) the presence of *Klebsiella pneumoniae* in the water source, was associated with lower goiter prevalence but, contamination of the pipeline system (households and schools) with gram-negative bacteria was associated with higher disease rates. Resorcinol is goitrogenic in man and experimental animals. Phthalate esters, also related to humic materials, undergo biodegradation by gram-negative bacteria with production of intermediate metabolites possessing anti-thyroid activity. Like phthalates and resorcinol, organic disulfides have also been identified as water contaminants in other parts of the world, and are known to be potent anti-thyroid compounds.

2-THIOCYANATE

To utilize the antibacterial effect of the lactoperoxidase system to prevent bacterial spoilage of raw milk it is necessary to increase the thiocyanate concentration of the milk. Thiocyanate has, however, a potent antithyroid effect which is enhanced by iodine deficiency (3).

The mean serum thiocyanate level of 3.2 mg/l in goitrous subjects from rural Darfur was significantly higher than the values of 1.7 mg/l in non-goitrous subjects from Khartoum (4). In vitro studies thiocyanate concentrations equivalent to serum levels of smokers (5) showed three independent antithyroid actions: (i) inhibition of iodide transport, (ii) inhibition of iodine organification, and (iii) increased iodide efflux. Inhibition of iodide transport by thiocyanate was competitive with iodide and independent of TSH concentration.

3-ANIMAL FEEDING PATTERN

Dependent on the species, feedstuffs and plants differ considerably in their iodine content. Among the iodide poorest feedstuffs there are grain concentrates, extracted soybean and rapeseed oil meals, mixed feed (without I-containing mineral mixture) and grasses. The iodide content of the plants decreases with proceeding growth. The iodide intake of ruminants via vegetable feed and drinking water is affected by the distance of the site from the seaside and the geological origin of the soil material. Therefore, mineral mixtures for cattle and sheep will affect finally the iodine intake of the population (6).

In the southern districts of Germany the calculated iodine uptake of adults was 80 micrograms/day before the iodine supplementation of the mixtures of mineral substances and the packet kitchen salt. The iodine supplementation of the mixtures of mineral substances for cattle and pig tripled the iodine content of the milk and doubled the proportion of iodine of the meat, the inner parts and the sausage produced from them (7).

4-MILLET

Pearl millet [*Pennisetum millet* (L.) leeke] is the main source of food energy for the rural poor in many areas of the semiarid tropics. Epidemiological

evidence suggests that millet may play a role in the genesis of endemic goiter in these areas, and sparse experimental data in rats support this suspicion. Thus, in vivo and in vitro studies revealed that millet diets rich in C-glycosylflavones produce goitrogenic and antithyroid effects similar to those of certain other antithyroid agents. In areas of iodine deficiency in which millet is a major component of the diet, its ingestion may contribute to the genesis of endemic goiter (8).

5-POLLUTANTS

Pollutants(9) that cause goiter are known as environmental goitrogens which may cause the condition by acting directly on the thyroid gland but also indirectly by altering its regulatory mechanisms and the peripheral metabolism and excretion of thyroid hormones. However, the mechanism that induces the trophic changes leading to goiter formation, and in some instances with hypothyroidism, is not well understood. Antithyroid compounds may enter into the water, air and food exposure pathways, becoming an important environmental goitrogenic factor in man and other animals. In iodine-sufficient areas, these compounds may be responsible for the development of some "sporadic" goiters or the persistence of the goiter endemic with its associated disorders.

6-VEGETABLES

Vegetables from the Cruciferae family, chronic consumption of poorly detoxified cassava containing large amounts of cyanogenic glucosides, flavonoids, humic substances originating from the organic residues in the soil are clearly involved in the etiology of endemic goiter (10).

7-IODINE

Iodine deficiency remains the main goitrogenic factor which affects not only many developing countries, but still many areas in Western Europe. Iodine excess is much less often responsible for the development of goiter, but through the iodine-induced immune disturbances within the thyroid, could on a long run, appear also goitrogenic (11).

Thyroid function tests should be monitored routinely if iodine is applied as a topical antiseptic (Betadine) to infants (12).

8-BROMIDE

Thyroid peroxidase and lactoperoxidase are capable of producing oxidized bromine species, in vivo bromination of tyrosyl residues in thyroglobulin might be of some importance in cases of either iodine deficiency or excessive bromide intake (13). Bromide toxicity is dependent upon the state of the iodine supply, which should be taken into account for evaluation of acceptable daily intake values for bromide (14).

9-AUTOIMMUNE PHENOMENA

The goitrogenic role of autoimmune phenomena in endemic goiter is still uncertain. Scanty and discrepant results have been reported in different areas of the world. . These data suggest that autoimmune phenomena are of limited importance in the development of endemic goiter (15, 16).

10-FLUORIDE

The increasing use of fluoride for prevention of dental caries poses the problem as to whether this halogen has antagonistic properties towards iodine, whereby it could hamper the success of iodine prophylaxis of endemic goiter. Published data failed to support the view that fluoride, in

doses recommended for caries prevention, adversely affects the thyroid (17).

11-NITRATE

The effect of nitrate contamination of drinking water on volume and function of the thyroid in human populations exposed to different nitrate levels in their drinking water was studied (18). A dose-dependent difference in the volume of the thyroid was observed between low and medium vs. high nitrate exposure groups, showing development of hypertrophy at nitrate levels exceeding 50 mg/l. An inverse relationship was established between the volume of the thyroid and serum thyroid stimulating hormone (TSH) levels.

12-SELENIUM

Selenium is a trace element essential for the activity of type I 5'-deiodinase which converts thyroxin (T4) to 3,5,3'-triiodothyronine (T3). In iodine deficient hypothyroid children at low selenium dietary intake the supplementation of selenium induced a significant decrement of serum FT4 and T4 concentrations and an increase of serum TSH concentrations (19). Several hypotheses concerning consequences of selenium deficiency on iodine metabolism can be proposed on the basis of experimental studies in rats and from epidemiological and experimental studies in humans. By decreasing intracellular GSH peroxidase activity, selenium deficiency may increase hydrogen peroxide (H₂O₂) supply and lead over several weeks to the thyroid atrophy observed in myxoedematous cretins. By improving thyroid hormone synthesis and by decreasing peripheral thyroxin (T4) deiodination, **selenium deficiency could protect fetal brain T4 supply and thus prevent neurological cretinism (20). One effect of selenium deficiency may be to lower glutathione peroxidase activity in the thyroid gland, thus allowing hydrogen peroxide produced during thyroid hormone synthesis to be cytotoxic. In selenium and iodine deficient humans, selenium supplementation may aggravate hypothyroidism by stimulating thyroxin metabolism by the selenoenzyme type I iodothyronine 5'-deiodinase.** Selenium supplementation is thus not indicated without iodine or thyroid hormone

supplementation in cases of combined selenium and iodine deficiencies (21). In northern Zaire (22), a selenium supplementation trial has been conducted. Besides correcting the GPX activity, two months of selenium supplementation was shown to modify the serum thyroid hormones parameters in clinically euthyroid subjects and to induce a dramatic fall of the already impaired thyroid function in clinically hypothyroid subjects. In an iodine deficient area, this selenium deficiency could lead to opposite clinical consequences: protect the general population and the fetus against iodine deficiency and brain damage; and in turn, favor the degenerative process of the thyroid gland leading to myxoedematous cretinism.

13-TOXOPLASMOSIS

The possible association between iodine deficiency and toxoplasma infection was reported in one preliminary study with a significant difference in the prevalence of toxoplasmosis in children with grade II goiter and grade I or no goiter (23).

14-DRUGS

Many goitrogenic drugs (24) exert a direct effect on the thyroid gland to disrupt one of several steps in the biosynthesis and secretion of thyroid hormones. This includes **1) inhibition of the iodine-trapping mechanism (thiocyanate or perchlorate), 2) blockage of organic binding of iodine and coupling of iodothyronines to form thyroxin (T4) and triiodothyronine (T3) (e.g., sulfonamides, thiourea, methimazole, and aminotriazole, among others), and 3) inhibition of thyroid hormone secretion by an effect on proteolysis of active hormone from the colloid (lithium or an excess of iodide).** Another large group of goitrogenic chemicals disrupts thyroid hormone economy by increasing the peripheral metabolism of thyroid hormones through an induction of hepatic microsomal enzymes. This group includes CNS-acting drugs (**phenobarbitone, benzodiazepines**), **calcium channel blockers (nicardipine, nifedipine), steroids (spironolactone), retinoids, chlorinated hydrocarbons (chlordane, DDT, TCDD), polyhalogenated biphenyls (PCB, PBB), and enzyme inducers.** Thyroid hormone economy also can be disrupted by xenobiotics that inhibit the

5'-monodeiodinase, which converts T4 in peripheral sites (e.g., liver and kidney) to biologically active T3. Inhibition of this enzyme by amiodarone, and iopanoic acid lowers circulating T3 levels, which results in a compensatory increased secretion of thyroid-stimulating hormone (TSH). Amiodarone treatment in an iodine deficient area as above should be judiciously decided and thyroid function carefully monitored before and during the use of the drug (25).

IV-IODINE EXCESS

Iodine is a requisite substrate for the synthesis of the thyroid hormones, the minimum daily requirement being about 50 micrograms.

An auto-regulatory mechanism within the thyroid serves as the first line of defense against fluctuations in the supply of iodine and also permits escape from the inhibition of hormone synthesis that a very large quantity of iodine induces (Wolff-Chaikoff effect).

Iodination program prevents the pathologic consequences of cretinism and reduces the frequency of the other pathologic consequences of iodine deficiency. Iodine excess results principally from the use of

iodine-containing medicinal preparations or radiographic contrast media.

The pathologic consequences of iodine excess will ensue only when thyroid auto-regulation is defective, in that escape from the Wolff-Chaikoff effect cannot occur, or when auto-regulation is absent.

Defective auto-regulation characterizes the **fetal and neonatal thyroid**, Hashimoto's thyroiditis, radioiodine or surgically treated Graves' hyperthyroidism, the thyroid of patients with cystic fibrosis, and the thyroid that has been exposed to weak inhibitors of the organic binding of iodine. In these circumstances, the provision of excess iodine may lead to iodide goiter with or without hypothyroidism. Absent autoregulation may be a feature of long standing multinodular goiter, and the provision of excess iodine in this circumstance may induce thyrotoxicosis (Basedow disease). The pathologic consequences of iodine excess will resolve when the source of iodine has been dissipated. In addition to its role in reversing iodine deficiency, iodine is used as adjunctive therapy for hyperthyroidism. By inhibiting the proteolytic release of iodothyronines from thyroglobulin, it induces a prompt slowing of thyroid hormone secretion. This effect is

exploited in the treatment of thyrotoxic crisis or severe thyrocardiac disease. Iodine also reduces thyroid cellularity and vascularity and therefore is used in the preparation of the patient for thyroidectomy. Finally, by exploiting the failure of escape from the Wolff-Chaikoff effect, iodine may also be used in the early management of radioiodine-treated Graves' hyperthyroidism. In a limited number of places excessive iodine from seaweed used as staple food results in endemic goiter.

V-IODINE DEFICIENCY AND IMMUNITY

Protein-calorie malnutrition is associated with impaired immunocompetence and increased susceptibility to infection. Zinc undernutrition results in lymphoid atrophy and reduced capacity to respond to many T-cell-dependent antigens. Iron deficiency results in a slight decrease in the number of rosette-forming T cells and a significant impairment of lymphocyte response to mitogens and antigens. Polymorphonuclear leukocytes are unable to kill ingested bacteria and fungi in an efficient manner. Copper deficiency impairs cell-mediated immunity, as does selenium deficiency when it is associated with vitamin E lack (26). An adequate iodine intake is necessary for normal retarded immune response. The molecular mechanism by which iodine increases immune response is still to be decided (27).

VI-MATERNAL FETAL RELATION-IN IDD SITUATIONS

1-THYROID FUNCTION IN NORMAL PREGNANT WOMEN

In healthy pregnant women, the regulation of thyroid function depends upon several factors. **Three factors act independently to increase thyroid hormone requirements:**

- 1) The marked **increase in the binding capacity of serum due to high TBG levels;**
- 2) The **direct stimulation of the thyroid by human chorionic gonadotropin**, acting as a thyrotropic hormone.
- 3) The **increase in placental deiodinating activity**, which may contribute to modify thyroid hormone metabolism.

These stimulatory events result in a physiological adaptation of the maternal thyroid gland to pregnancy, as long as the availability of iodine for the thyroidal "machinery" remains sufficient. In areas where the iodine intake is at the lower limit of the needs for healthy non pregnant adult subjects (less than 100 micrograms/day), decreased iodine availability during gestation leads to relative iodine deficiency and hence, pregnancy constitutes a "challenge" for the thyroid gland.

Thyroid volume does not increase during pregnancy in iodine-replete areas (28). The decrease in free T4 and free T3 and the increase in free reverse T3 concentrations during pregnancy resemble the changes in thyroid hormones seen in non-thyroidal illness. This could be a physiological adaptation enabling energy conservation during the high metabolic demands of pregnancy.

A clinically detectable increase in thyroid size has been found in areas of mild iodine deficiency ('goiter of pregnancy'), but not in iodine replete areas. It was shown that excessive thyroidal stimulation occurred in as much as one third of pregnancies in Brussels, accompanied by relative hypothyroxinemia, marked elevation in serum TG levels and goitrogenesis. About 10% of women had developed a goiter at parturition, which was only partially reversible during the postpartum period (29).

In iodine deficient area the thyroid is subjected, during pregnancy to increased demands which is associated with a tendency to endogenous iodine deficiency. Under the conditions of insufficient iodine supply the pathophysiological changes result in: 1) prevalence of goiter in about 60% of pregnant women; 2). enlargement of the extent of neck in more than 50% of all pregnant women examined only returning to the pre-pregnant status in 25%-40%; and 3) a prevalence of goiter in newborn with 5%;.(30,31)

2-FETAL and MATERNAL THYROID HORMONES

It is well known that insufficient production of thyroid hormones during the fetal and neonatal period of development may result in permanent brain

damage unless treatment with thyroid hormone is instituted very soon after birth.

Congenital hypothyroidism is not the only situation in which brain damage may be related to insufficient thyroid function.

Cretinism is the most severe manifestation of iodine deficiency disorders found in areas where iodine intake is greatly reduced. Some of the manifestations of cretinism suggest that the insult to the developing brain starts earlier than in the case of congenital hypothyroidism.

Maternal hypothyroxinemia due to endemic iodine deficiency is associated with an increased incidence of neurological disorders in the offspring. Such correlations were originally postulated as reflecting direct effects of elemental iodine on fetal brain development during early pregnancy, it was generally believed that maternal thyroid hormones do not cross the placenta in significant amount as a result of elevated concentrations of TBG in maternal blood. However TBG possesses the capacity to enhance T4 transport to particular target organs during pregnancy.

Maternal T4 is transported to the fetus, and is of crucial importance to early fetal development, and TBG forms part of a control system specifically designed to maintain at an optimal level the T4 environment to which the developing fetus is exposed.

Subsequent studies in rats demonstrated that maternal T4 traverses the placenta in significant amounts prior to the development of the fetal thyroid. Other studies have led to suggest that one or more isoforms of HCG may be implicated in a feed-back system interacting with the hypothalamic/pituitary system governing maternal thyroid hormone secretion. Fetal exposure to maternal hormones is likely under placental control, and that other components of this putative system are worthy of study.

For these reasons the possible role of maternal transfer of thyroid hormones during early fetal development have been reinvestigated, using the rat to obtain various experimental models. It has been shown that thyroid hormones are found in embryonic tissues before onset of fetal thyroid function and that thyroidectomy of the mother results in delayed development of the concepta. The concentrations of T4 and T3 in embryonic tissues from thyroidectomized dams were undetectable before the onset of fetal thyroid function, and still reduced in some tissues near term, despite the onset of fetal thyroid function. Treatment of control and

thyroidectomized dams with methyl-mercaptoimidazole to block fetal thyroid function reduced thyroid hormone concentrations in fetal tissues near term, but this decrease could be partially avoided by infusion of physiological doses of thyroxin to the mothers. Iodine deficiency of the mothers resulted in thyroid hormone deficiency of the developing embryo, which was very marked until term in all tissues including the brain. The results strongly support a role of maternal thyroid hormones in fetal thyroid hormone economy both before and after the onset of the fetal thyroid function, at least in the rat. They also support a role of the hypothyroxinemia of iodine-deficient mothers in initiating the brain damage of the endemic cretin, a damage which would not be corrected once the fetal thyroid becomes active, as iodine-deficiency of the fetus would impair adequate production of hormones by its own thyroid, and maternal transfer would continue to be low (32).

Maternal thyroid hormone levels during pregnancy from a severely iodine deficient region showed a significant correlation between Thyroxin (and not T3) level and the subsequent cognitive and motor performance of the children examined at the age of 10-12 years (33). It is speculated that maternal thyroxin and not triiodothyronine may be essential for normal neurological maturation of the fetus before the fetal thyroid becomes functional.

3-NEONATAL HYPOTHYROIDISM

The present data indicate that in **newborn from areas of iodine deficiency there is a higher frequency of elevated TSH levels and low T4 values than is found in areas where iodine intake is normal.** This frequency is correlated to the degree of the iodine deficiency. The data suggest that **the impairment of thyroid function at birth may be a transient phenomenon. The duration and the severity of the transient neonatal hypothyroidism, however, is greatly variable and its evolution unpredictable.**

The incidence of Congenital Hypothyroidism detected by screening is about 1 in 4000 births in North America, Europe and Australia; it is lower (1 in 7000) in Japan. The etiology remains unknown; genetic and environmental factors are possibly involved. The role of autoimmunity has recently been studied extensively. Antithyroglobulin (ATA) and

antimicrosomal antibodies are not involved; the possible role of thyroid growth blocking antibodies (TGAb) of maternal origin remains controversial. Evaluation of clinical signs, bone maturation, serum T4 and the position and size of the thyroid by scintigraphy at the time of diagnosis in CH infants are important because these variables are related to the final psychoneuro-intellectual prognosis, irrespective of the adequacy of therapy. Thyroid ultrasonography always distinguishes a normal thyroid in the neonate but cannot define precisely the type of thyroid dysgenesis, if present (e.g. ectopic, athyreosis). The determination of serum Tg contributes to the diagnosis but its specificity and sensitivity are insufficient to replace thyroid scintigraphy. Therapy by LT4, at an initial dose of 25-50 micrograms/day in full-term infants, is universally recommended. The objective of therapy is to reach as soon as possible and to maintain serum concentrations of total and free T4 at the upper limits of normal for age. Serum TSH should decrease as rapidly as possible below 20 microU/ml and then remain within the normal range. Persistent hyperthyrotropinaemia in spite of normal serum T4 has to be avoided as it could represent poor compliance and/or insufficient therapy. Programs of 10 to 14 years of follow-up of CH infants have now shown that the neuropsychointellectual prognosis of CH is excellent in all cases when therapy and psychosocial environment are adequate. Although still within the normal range, IQ is somewhat lower in spite of appropriate therapy in cases of severe prenatal hypothyroidism and some transient and correctable neurological signs occasionally occur. In Western countries transient neonatal hypothyroidism is usually due to iodine deficiency or iodine excess; the newborn infant is hypersensitive to the antithyroid action of an extraphysiological supply of iodine. TSH binding inhibitor immunoglobulin (TBII) of maternal origin occasionally cause transient neonatal hypothyroidism.

In developing countries with severe iodine deficiency and endemic goiter, the incidence of thyroid failure in the newborn can be as high as 1 in 10.

4-IODINE DEFICIENCY AND NEONATAL THYROID SCREENING

A multicentric pilot screening program for congenital hypothyroidism and comparison between the results obtained from areas characterized by low

iodine supply and endemic goiter, and, a non-endemic area, was reported from Italy. **A shift of TSH at screening toward higher values as well as a higher percentage of recall from low iodine supply and endemic goiter area was observed (34). This finding emphasizes the importance of screening for congenital hypothyroidism as a suitable index of the presence and action of goitrogenic factors in the environment.**

The frequency of "false positive" cases (recall for values of 30 mU/L of TSH in whole blood) in the different **geographic regions of Greece showed wide variation between the south and the north areas of the country. It was suggested that these differences reflect the degree of iodine deficiency in the population and may be used as an epidemiological indicator of this deficiency (35).**

A low iodine supply in newborn populations was accompanied by, and probably explained by an elevated frequency of transient disorders of thyroid function in young infants (36). Iodine prophylaxis is needed in some areas not only for the prevention of goiter, but mostly for the prevention of impairment of thyroid function during the critical period of brain development.

5-IODINE SUPPLEMENTATION DURING PREGNANCY

Much has been learned during the past several decades about the role of nutrition in the course and outcome of pregnancy. It is generally appreciated at the present time that the fetus is not a "perfect parasite"; maternal stores can be drawn upon for support but a limit exists as to the ability of the fetus to drain maternal supplies. Reduced maternal thyroid hormone concentrations during pregnancy can adversely affect fetal neurological development.

In the context of national iodine supplementation programs, concern has been expressed over the theoretical possibility that iodine supplementation during pregnancy might adversely affect fetal development as a result of maternal thyroid inhibition from the Wolff-Chaikoff effect. Several measures of motor and cognitive function showed no significant differences at either age 11 or 15 years between those children whose mothers had received supplementary iodine during pregnancy and the control children whose mothers had received the placebo (37).

Cord blood Tg was much lower when the mother had received iodine, whereas TSH, T4, T3, and free T4 levels were unaltered (38).

Iodine requirements are increased during pregnancy and lactation and adequate iodine intake is important for normal brain development of the fetus/newborn child. It seems reasonable, according to a Danish study, to recommend a high intake of food containing iodine (e.g. milk products) during pregnancy and lactation (39).

Iodoprophylaxis should be warranted even in areas with moderate iodine deficiency to prevent the increase in thyroid size and, probably, to avoid the risk of maternal and fetal hypothyroidism (40).

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