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## Hypothyroidism and Thyroid Function Alterations During the Neonatal Period

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### 1. Introduction

The thyroid hormones, T<sub>4</sub> and 3,5,3'-triiodothyronine (T<sub>3</sub>), are necessary for adequate growth and development (Greenberg AH et al., 1974; Zimmermann, 2011), throughout fetal and extrauterine life. These hormones regulate many metabolic processes: somatic growth, cardiac, pulmonary and bone maturation, central nervous system maturation, and neuronal differentiation, regulate oxygen consumption, and protein, lipid and carbohydrate metabolism. There is evidence that thyroid hormones are necessary for surfactant synthesis and lung maturation (Biswas S et al., 2002). Brain and lung maturation have received special attention, because of the potentially irreversible or life-threatening consequences associated with early thyroid hormone deficiency (Kester MA et al., 2004; De Vries et al., 1986). The importance of thyroid hormones to perinatal neural development is well established but their relation to the developmental sequelae of preterm birth is being recently studied. During the first half of gestation the thyroid hormone available to the fetus is predominantly of maternal origin. T<sub>4</sub> from the mother is the most important source of T<sub>3</sub> for the fetal brain and protects it from a possible hormone deficiency until birth. Once fetal thyroid secretion starts, fetal supplies are of mixed fetal and maternal origin. Although fetal thyroidal secretion is believed to constitute an increasing proportion of the hormone available to the developing fetus, maternal transfer of T<sub>4</sub> may still contribute significantly to fetal needs (20-50% of normal values) up to term, mitigating the consequences of inadequate fetal thyroid function. The transfer of iodine is also difficult to quantify, but the iodine content of the fetal thyroid increases progressively from less than 2 µg at 17 weeks of gestation up to 300 µg at term (Figure 1). Thyroid function in premature infants is immature at birth. Preterm infants often have low thyroxine (T<sub>4</sub> and FreeT<sub>4</sub>) levels postnatally, a condition referred to as transient hypotiroxinemia of prematurity. Transient hypotiroxinemia can be found in approximately 35% of all premature newborns and in 50% babies born with less than 30 weeks. This occurs during an important period for brain development and low T<sub>4</sub> levels

could be a negative factor contributing to the neurodevelopment problems of very preterm infants. The number of extremely low birth weight babies (ELBW) is high. Interventions have increased the population at risk. The precocious diagnosis and treatment of the alterations of thyroid function during the neonatal period, could have beneficial effects in the prevention of developmental abnormalities. Iodine is a trace element which is essential for the synthesis of thyroid hormones. The iodine intake of newborns is entirely dependent on the iodine content of breast milk and the formula preparations used to feed them. An inadequate iodine supply (deficiency and excess) might be especially dangerous in the case of premature babies. The minimum recommended dietary allowance (RDA) is different depending on age groups. The iodine intake required is at least  $15 \mu\text{g}/\text{kg}/\text{day}$  in full-term infants and  $30 \mu\text{g}/\text{kg}/\text{day}$  in preterms. Newborn infants are in a situation of iodine deficiency, precisely at a stage of psychomotor and neural development which is extremely sensitive to alterations of thyroid function ( Ares et al., 1994, 1995, 2004, 2005, 2007; Zimmermann MB, 2004, 2009 )

## 2. Thyroid function in the fetus and newborn

$T_4$ , free  $T_4$  ( $FT_4$ ) and  $T_3$  of preterm and term neonates increased with PMA, whereas thyroglobulin (Tg) decreased and thyroid-stimulating hormone (TSH) did not change. Serum  $FT_4$ ,  $T_3$ , Tg and TSH of neonates were affected negatively, independently of age, by different neonatal factors, including a low iodine intake. It is often presumed that the low thyroxine levels in premature infants are a continuation of levels experienced in utero, a

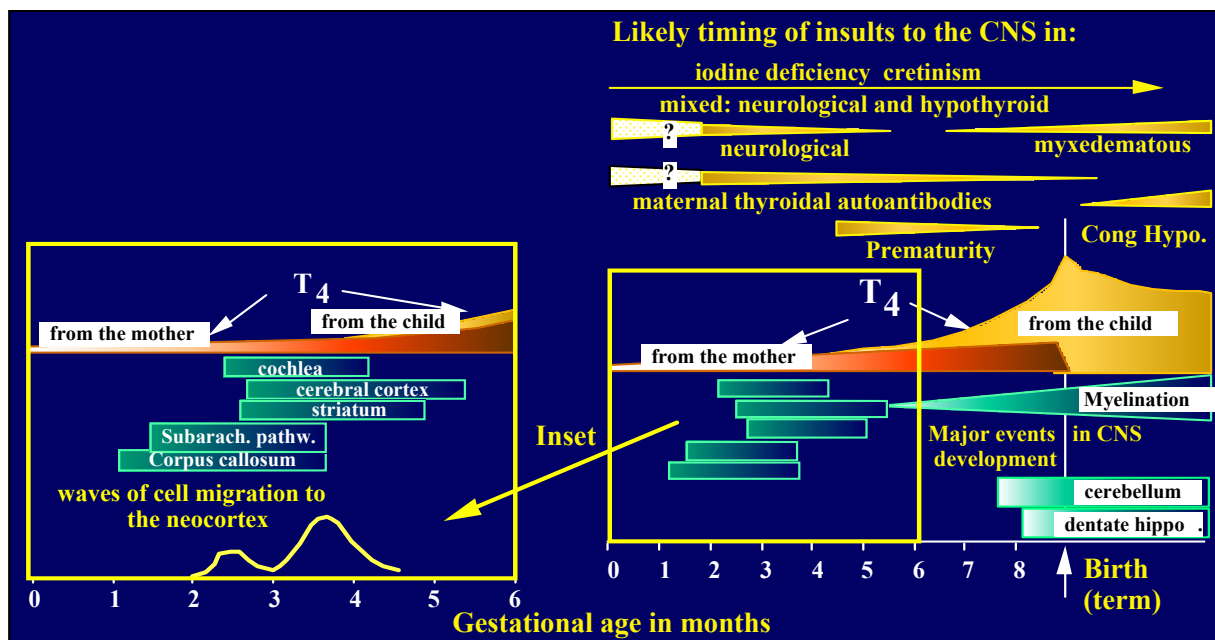


Fig. 1. Shows the overlapping changes in input thyroid hormones in utero and postnatally immediately with the start of important phases of development human brain during pregnancy. At the top  $T_4$  represents the amount needed by the fetus that is entirely from maternal origin until the middle of the pregnancy, and maternal origin and fetal thereafter. They represent only the needs of  $T_4$ , and from it derives the brain  $T_3$  during these phases of development.

condition referred to as transient hypothyroxinemia of prematurity, but data derived from blood obtained by cordocentesis have shown that TSH and T4 levels sampled from fetuses are higher than those found in premature infants of the same gestational age (Figure 2). Neonatal alterations in thyroid function and hypothyroxinemia of prematurity are thought to be caused by several reasons. These include the incomplete maturation of the hypothalamic-pituitary-thyroid axis and relative immaturity of the type I iodothyronine deiodinase enzyme systems, the untimely interruption of maternal transfer of thyroid hormones to the fetus across the human placenta, maternal antibodies, postnatal drugs (dopamine, heparine, corticoids...) and neonatal disease. Quite prominent among these causes are iodine deficiency during gestation and the neonatal period, and peri- and post-natal exposure to an iodine excess, usually caused by iodine-containing antiseptics and radiologic contrast media. The percentage contribution of iodine deficiency to thyroid dysfunction may be greater in the more immature infants who have a very low iodine supply: Serum FT4, T3, Tg and TSH of preterm neonates were affected negatively, independently from age, by a low iodine intake. Iodine deficiency contributes to about 30% of the hypothyroxinaemia in enterally and parenterally fed preterm infants of 27–30 weeks gestation (Morreale G 1990, Morreale G 2002, Delange 2001, 2004, Fisher 1969, 1970, 1981)

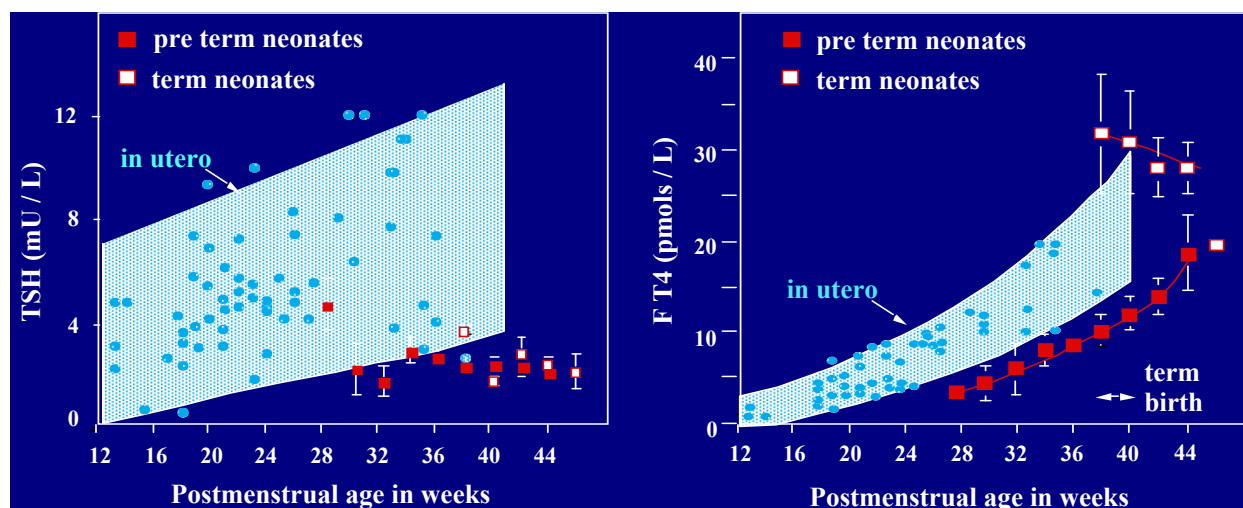


Fig. 2. Concentrations of FT4 of preterm and term neonates are superimposed on data published for fetuses in utero (by Thorpe-Beeston et al.1991) The shaded area corresponds to the 95 % confidence intervals for the fetal FT4 and TSH data (G Morreale de Escobar, S Ares 1998).

### 3. Iodine requirements during the first month of life

Iodine is a trace element which is essential for the synthesis of thyroid hormones. If maternal iodine deficiency in pregnancy is severe, fetal brain damage will occur. This damage is irreversible after birth. Mild/moderate iodine deficiency during pregnancy and early postnatal life is associated with neuro/psycho-intellectual deficits in infants and children. The severity is not only related to the degree of iodine deficiency, but also to the developmental phase during which it is suffered, the most severe being the consequence of iodine deficiency during the first two trimesters of pregnancy. An inadequate iodine supply might be especially dangerous in the case of premature infants, who are prematurely

deprived of the maternal supply of hormones and iodine, before their own gland has been able to accumulate as much iodine as in term newborns. The iodine intake of newborns is entirely dependent on the iodine content of breast milk and the formula preparations used to feed them. The minimum recommended dietary allowance (RDA) for different age groups has recently been revised. Taking into consideration new information regarding iodine metabolism in premature and term newborn infants, to meet such requirements the iodine content of formulas for premature newborns should contain 20  $\mu\text{g}/\text{dl}$ , and that of first and follow-up preparations 10  $\mu\text{g}/\text{dl}$ . We refer here to these new recommendations as those of the ICCIDD (International Council for the Control of Iodine Deficiency Disorders). The availability of iodine during the peri- and post-natal period of development should both ensure the minimal requirements and should not exceed the minimum amounts blocking their thyroid function. The requirement of iodine in neonates was evaluated from metabolic studies. To reach adequate intake the iodine content of formulas for premature newborns ought to contain 20  $\mu\text{g}/\text{dl}$ , that of all other preparations 10  $\mu\text{g}/\text{dl}$ . The recommended intake of iodine in neonates reflects the observed mean iodine intake of young infants exclusively fed human milk in iodine replete areas. However, it is well established that the iodine content of breast milk is critically influenced by the dietary intake of the pregnant and lactating mother (Delange F et al., 1985b; Delange F et al., 1993; Semba RD, 2001; Dorea JG, 2002). The iodine requirement in neonates was evaluated from metabolic studies by determining the values which resulted in a situation of positive iodine balance, which is required in order to insure a progressively increasing intrathyroidal iodine pool in the growing young infant (Delange F et al., 1993). In our unit we studied thyroid gland volume by ultrasound and we found that the volume varied from 0.3-1.3 ml in preterm infants during the first month of life and 0.9 ml in term infants at birth (Ares S et al., 1995). These studies indicate that the iodine intake required in order to achieve a positive iodine balance is at least 15  $\mu\text{g}/\text{kg}/\text{day}$  in full-term infants and 30  $\mu\text{g}/\text{kg}/\text{day}$  in preterms. This corresponds approximately to 90  $\mu\text{g}/\text{day}$  and is consequently twice as high as the 1989 recommendations of 40-50  $\mu\text{g}/\text{day}$  (National Research Council, 1999; Delange F, 2004).

#### 4. Iodine deficiency

Iodine is a trace element that is essential for the synthesis of thyroid hormones. An inadequate iodine supply (deficiency and excess) might be especially dangerous in the case of premature babies. The minimum recommended dietary allowance is different depending on age groups. Premature infants are in a situation of iodine deficiency, precisely at a stage of psychomotor and neural development that is extremely sensitive to alterations of thyroid function. The iodine intake does affect the circulating levels of FT<sub>4</sub>, T<sub>3</sub>, Tg and TSH in preterm infants, independently of their age. Circulating levels are lower in preterm than in term neonates of comparable age and iodine intake (or balance), at least up to 44 weeks PMA and an intake of 80  $\mu\text{g}/\text{day}$ . T<sub>4</sub>, free T<sub>4</sub> (FT<sub>4</sub>) and T<sub>3</sub> of preterm and term neonates increased with age, whereas thyroglobulin (Tg) decreased and thyroid-stimulating hormone (TSH) did not change. Serum FT<sub>4</sub>, T<sub>3</sub>, Tg and TSH of preterm neonates were affected negatively, independently of age, by a low iodine intake. The percentage contribution of iodine deficiency to hypothyroxinaemia may be greater in the more immature infants who have a very low iodine supply: Serum FT<sub>4</sub>, T<sub>3</sub>, Tg and TSH of preterm neonates were

affected negatively, independently from age, by a low iodine intake. Iodine deficiency contributes to about 30% of the hypothyroxinaemia in enterally and parenterally fed preterm infants of 27–30 weeks gestation (Figure 1 and Figure 2) (Ares S et al., 1994; Ares S et al., 1995; Ares S et al., 1997; Morreale de Escobar G et al., 1998; Ares S et al., 2004).

## 5. Iodine excess

In normal individuals, the acute and chronic excess of iodine rarely leads to profound clinical thyroid dysfunction, because of the rapid activation of several autoregulatory mechanisms. However, in some individuals, such as newborns, the escape from the inhibitory effect of large doses of iodine is not achieved and clinical (symptomatic hypothyroidism) or subclinical hypothyroidism (asymptomatic hypothyroidism or altered serum thyroid parameters) The most frequently identified sources of excess iodine leading to problems in neonates result from the use of iodine-containing disinfectants (10,000 microg of iodine/mL) and from radiograph contrast media (250-370 mg of iodine/mL) given for radiological examination. The total concentration of iodine in plasma comprises the iodine in circulating T<sub>4</sub> and T<sub>3</sub>, plus the circulating iodide and any iodine contained in contrast media, or other contaminating compounds. The minimum amount of iodine that can cause a Wolff–Chaikoff effect in premature and term neonates has not been clearly defined, as it may depend on a variety of factors, including the chemical form in which the iodine overload is supplied (Wolff J, Chaikoff IL, 1969; Ares et al., 2008 ). There is a marked individual variability in the sensitivity to iodine-overload. Urinary iodine concentrations above 16 microg/dL, 20 microg g/dL, and 25 microg g/dL may impair thyroid function in neonates. Some iodinated contrast agents, such as ipodate and iopanoic acid, are well-known inhibitors of all known iodothyronine deiodinases.

## 6. The role of thyroid hormones on human central nervous system during fetal and postnatal life

The close involvement between human brain development and thyroid hormones is widely accepted (Morreale de Escobar G et al., 2000, 2004). The effects of T<sub>3</sub> on the central nervous system are mediated by the regulation of the expression of genes that synthesize proteins implicated in cerebral neurogenesis, neuronal migration and differentiation, axonal outgrowth, dendritic ontogeny, and synaptogenesis. They are also necessary for cerebellar neurogenesis (predominantly during early postnatal life), gliogenesis (predominantly during late fetal life to 6 months postnatally), and myelogenesis (during the second trimester of gestation to 2 years of postnatal life). Low T<sub>4</sub> levels during neonatal life, especially if persistent, could be a negative factor contributing to the neurodevelopmental problems of very preterm infants. Indeed, retrospective studies have shown a relationship between hypothyroxinemia and developmental delay and an increased risk of disabling cerebral palsy (De Vries et al., 1986; den Ouden AL et al., 1996; Lucas A et al., 1988, Lucas A et al., 1996; Meijer WJ et al., 1992; Lucas A et al., 1996; Reuss ML et al., 1996).

## 7. Alterations of the thyroid function during the neonatal period risk factors

There are many more associations of postnatal factors with transient alterations of thyroid function than had previously been considered in newborn infants. A oblique preventative

approach may be necessary through reduction in the incidence or severity of individual illness(es). Similarly, alternatives to those drugs that interfere with the hypothalamic-pituitary-thyroid axis should be evaluated (e.g. other inotropics instead of dopamine) (Table 1 and 2)

<ol style="list-style-type: none"> <li>1. Abrupt withdrawal of maternal iodine, T<sub>4</sub> and TRH from placenta.</li> <li>2. The adaptive response of the thyroid axis at the interruption of the placental circulation is insufficient.</li> <li>3. Incomplete development of the hypothalamic-pituitary-thyroid axis:             <ul style="list-style-type: none"> <li>• Insufficient secretion of TRH</li> <li>• Immature thyroid response to TSH</li> <li>• Lower retention of iodine in the thyroid. Inefficient Thyroglobulin Iodination until week 34.</li> <li>• Lower circulating levels of TSH, T<sub>4</sub>, FT<sub>4</sub>, T<sub>3</sub> and FT<sub>3</sub></li> </ul> </li> <li>4. Low synthesis and serum concentration of T<sub>4</sub> binding globulin (TBG)</li> <li>5. Underdevelopment of 5'DI -deiodinase, especially in the liver</li> <li>6. Decreased peripheral conversion of T<sub>4</sub> to T<sub>3</sub> in tissues</li> <li>7. Increased frequency of serious morbidity, and therapeutic management of drugs. Multiple influences over the hypothalamic-pituitary-thyroid axis.</li> <li>8. Frequent postnatal malnutrition</li> <li>9. Undetermined iodine intake and excretion.</li> <li>10. Iodine deficiency or excess.</li> </ol>
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Table 1. Causal factors of transient alterations of thyroid function in the preterm newborn.

### 7.1 Hypothyroidism in the newborn

Neonatal hypothyroidism is defined as decreased thyroid hormone production in a newborn. In very rare cases, no thyroid hormone is produced. In primary hypothyroidism, TSH levels are high and T<sub>4</sub> and T<sub>3</sub> levels are low. If the baby was born with the condition, it is called congenital hypothyroidism. If it develops soon after birth, it is called hypothyroidism acquired in the newborn period. Hypothyroidism in the newborn may be caused by: a missing or poorly developed thyroid gland, a pituitary gland that does not stimulate the thyroid gland or thyroid hormones that are poorly formed or do not work. The most common cause of hypothyroidism in the newborn is complete absence or underdevelopment of the thyroid gland. Endemic cretinism is caused by iodine deficiency, and is occasionally exacerbated by naturally occurring goitrogens. Dysgenesis of the thyroid gland, including agenesis (ie, complete absence of thyroid gland) and ectopy (lingual or sublingual thyroid gland) may be a cause. The incidence of congenital hypothyroidism, as detected through newborn screening, is approximately 1 out of every 3,000 births, but the incidence is different depending on the country, sex, race, ethnicity, gestational age,....

Girls are affected twice as often as boys. Less commonly, the thyroid gland is present but does not produce normal amounts of thyroid hormones. Although initial preliminary studies were performed using thyroid-stimulating hormone (TSH) levels in cord blood, mass screening was made feasible by the development of radioimmunoassay for TSH and thyroxine (T<sub>4</sub>) from blood spots on filter paper, obtained for neonatal screening tests. Some

infants identified as having primary congenital hypothyroidism may have transient disease and not permanent congenital hypothyroidism. Family history should be carefully reviewed for information about similarly affected infants or family members with unexplained mental retardation. Neonatal screening for congenital hypothyroidism in premature infants is not as well established as in term newborns regarding age and number of samples. Congenital hypothyroidism is more common in infants with birthweights less than 2,000 g or more than 4,500 g. and in multiple births. Inborn errors of thyroid hormone metabolism include dyshormonogenesis. Most cases are familial and inherited as autosomal recessive conditions. These may also include the following: thyroid-stimulating hormone (TSH) unresponsiveness (ie, TSH receptor abnormalities), impaired ability to uptake iodide, peroxidase, or organification, defect (ie, inability to convert iodide to iodine), Pendred syndrome, a familial organification defect associated with congenital deafness,

DRUG	METABOLISM	Thyroid function
Dopamine > 1 mcg / kg / min	Decrease: secretion of TSH	Decrease synthesis of thyroid hormones in the thyroid Decreased T4 and FT4
Fenobarbital	Increased metabolism of T4	Increased secretion of TSH in patients treated with T4
Glucocorticoides (dosis altas)	Increased secretion of TSH in patients treated with T4 Altered conversion of T4 to T3 decreased TBG, T3 and TSH	Decreased T <sub>4</sub> , T <sub>3</sub> and TSH
Furosemide	Decreases binding of T4 to TBG decreased T4, and increased FT4 Increases active lipoprotein lipase in plasma and	Decreases T4 and increased circulating FT4
Heparine	concentration of free fatty acids which displaces T4 from TBG and increases free T4	Decreases binding of T4 to TBG decreased T4, and increased FT4
Octotride		Decreased secretion of thyroid hormones in the thyroid decreased: T4, FT4 and increased TSH
Oral Iron sulfate	Inhibition of intestinal L-T4 absorption (when supplemented)	FT4 increased requirements in hypothyroidism

Table 2. Effects of some drugs used during the neonatal period on thyroid function.

Thyroglobulin defect (ie, inability to form or degrade thyroglobulin), Deiodinase defect. Thyroid hormone resistance (ie, thyroid hormone receptor abnormalities) may also be a cause. TSH or thyrotropin-releasing hormone (TRH) deficiencies are also noted. Hypothyroidism can also occur in TSH or TRH deficiencies, either as an isolated problem or in conjunction with other pituitary deficiencies (eg, hypopituitarism). If present with these

deficiencies, hypothyroidism is usually milder and is not associated with the significant neurologic morbidity observed in primary hypothyroidism. Initially, the newborn may have no symptoms. Later, the newborn may become sluggish (lethargic) and have a poor appetite, low muscle tone, constipation, a hoarse cry, and a bulging of the abdominal contents at the bellybutton (an umbilical hernia). The morbidity from congenital hypothyroidism can be reduced to a minimum by early diagnosis and treatment. Untreated infants will have delayed development, intellectual disability, and short stature. Because early treatment can prevent intellectual disability, all newborns should receive a screening blood test in the hospital early after birth to evaluate thyroid function. Many newborns with hypothyroidism require thyroid hormone given by mouth for their entire life. Treatment is directed by a doctor who specializes in treating children with problems of the endocrine system (a pediatric endocrinologist). (LaFranchi S 2001, LeFranchi S et al. 1977, La Franchi S 2011, Rovet JF 1999, Rovet JF 1999, Rovet JF et al. 2000)

## 7.2 Transient neonatal hypothyroidism

Transient hypothyroidism occurs when thyrotropin (TSH) levels are elevated but thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) levels are low but the thyroid gland is present, and there is another factor that causes this alteration. TSH usually increases when  $T_4$  and  $T_3$  levels drop. TSH prompts the thyroid gland to make more hormones. In subclinical hypothyroidism, TSH is elevated but below the limit representing overt hypothyroidism. Sometimes, the levels of the active hormones will be within the laboratory reference ranges. In maternal autoimmune disease, transplacental passage of antibodies cause transient or permanent hypothyroidism. Temporary hypothyroidism can be due to the Wolff-Chaikoff effect. A very high intake of iodine can produce a blockage in the synthesis of thyroid hormones. Although iodide is a substrate for thyroid hormones, high levels reduce iodide organification in the thyroid gland, decreasing hormone production. The antiarrhythmic agent amiodarone can cause hyper- or hypothyroidism due to its high iodine content. Iodine in contrast agents or skin disinfectants can cause hypothyroidism or hyperthyrotropinemia in premature neonates (Lopez -Sastre et al. 1999, Delange 1988, Webber G 1998).

## 7.3 Hyperthyrotropinemia

Physiologically, at birth occurs a sudden rise of TSH in normal newborns and premature infants, and the concentrations usually go down to within 1-2 weeks. Transient hyperthyrotropinemia is characterized the persistence of elevated TSH, but normal levels of  $T_4$ . The duration of the disorder varies from a few days to several months. The etiology is unknown in most cases (idiopathic). Occasionally, it appears as result of an excess of iodine or deficiency and is more frequent in preterm infants. Generally the disorder does not require treatment, but it must be monitored in order to exclude primary hypothyroidism. Hypothyrotropinemia occurs when thyrotropin (TSH) levels are elevated but thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) levels are normal. TSH prompts the thyroid gland to make more hormone. TSH is elevated but below the limit representing overt hypothyroidism. The levels of the active hormones will be within the laboratory reference ranges. Some infants will require thyroxine substitution therapy depending on the age, concomitant illness, TSh levels ... and should be evaluated individually.

#### 7.4 Hypothyroxinemia of prematurity

Transient hypothyroxinaemia of prematurity (THOP) is the most common thyroid dysfunction in preterm infants and is defined by temporary low levels of T4, T3 and normal or low TSH. Low T4 levels in preterm infants are associated with persistent neurodevelopmental deficits in cognitive and motor function. Thyroid hormone substitution trials to date are underpowered and show inconsistent results; the question remains that if low T4 levels simply an epiphenomenon or not. The aetiology of transient hypothyroxinaemia is multifactorial and the components amenable to correction form the basis of the therapeutic strategy: rectification of iodine deficiency in parenteral nutrition; a reduction of non-thyroidal illnesses and attenuation of their severity; and substitution of drugs that interfere with the hypothalamic-pituitary-thyroid axis. Thyroxine substitution therapy should only be done in the context of clinical trials and only in those infants who are severely hypothyroxinaemic. Some studies that investigated THOP and disabling cerebral palsy (CP) found an increased risk of CP in the 15% of infants < 33 weeks gestation who had the lowest thyroxine levels. A relative risk of 4 for CP translates into an etiologic fraction of 75%, and a population attributable risk of 31%. This means that 75% of all disabling CP in children with THOP, and nearly a third of disabling CP in all infants below 33 weeks gestation age are associated with low thyroid hormone levels. Approximately 20,000 births each year in the United States are of < 28 weeks gestation and 70% of them (~14,000) now survive. Approximately 12% of survivors (nearly 1,700 children) will have disabling cerebral palsy. In addition, several studies measured IQ or its equivalent, and found a reduction of 7-8 points (or more than half a standard deviation for the population) in children of mothers with subclinical hypothyroidism during pregnancy independently of THOP suggesting the problem may be more widespread. Thus, in theory, treatment of THOP alone could lead to the prevention of as many as 500-600 cases of CP in this gestational group. Paneth reviewed relationships among THOP, adverse neurological outcomes, and other perinatal variables, and described six different ways in which these sets of variables could be related to each other, only some of which implied a causal role for THOP in neurological adversity ( Paneth et al. 1998). However, unlike many other risk factors uncovered in population-based clinical research, this association is supported by a solid body of laboratory and clinical evidence, including the well-known adverse effects on the brain of thyroid and iodine deficiency. From population surveys, perinatal, developmental, human, animal and cell culture data, there is clearly a CNS "*window of vulnerability*" for brain damage in ELBW neonates. What is not yet known, and what cannot be established by any means other than a properly powered interventional trial, is whether the strong association of THOP with impaired neurodevelopment is in fact causal. Since previous work could not prove the need to treat due to sample size and concern that excessive treatment is itself a risk, outright intervention is not advocated at this time. On the other hand, if a physician were to choose to treat, we would recommend following a hospital-based structured protocol to *supplement* endogenous production without suppressing TSH release to enable future reflection on results rather than risk random intervention based on physician-to-physician bias (Van Wassenaer 1997, 1998, La Gamma 2006, 2009, Meijer WJ et al., 1992)

#### 7.5 Low T3 syndrome

In terms of fetal thyroid function, fetal T3 levels are low throughout gestation, and increase during the third trimester, reaching only 50% of adult levels, due to increased conversion of T4 in T3 inverse (rT3). The state of low concentrations of T3, often observed in newborns,

would be a reflection of fetal status. As in other ages, levels of T3 may fall in the presence of concomitant diseases and undernutrition. In some newborn infants hypoxemia, acidosis, hypocalcemia and infection, postnatal malnutrition have been found to be associated to low T3 levels by inhibiting the peripheral conversion of T4 to T3, leading to prolong (1-2 months at a time) the low values observed in adaptation to extrauterine life. Low serum total T3 is the most common abnormality in infants with neonatal illness, observed in about 70% of hospitalized patients. Serum total T3 levels can range from undetectable to normal in critically ill patients, with the mean total T3 level being approximately 40% of normal. It is believed that low serum T3 is a result of decreased production of T4, rather than increased degradation or increased disposal of T3. Unlike T4, which is produced solely in the thyroid, about 80% of circulating T3 is produced by extrathyroidal conversion of T4 to T3 by 5-monoiodinases present in organs such as the liver and kidney. Thus, there are two mechanisms by which T3 production may be reduced: decreased activity of the 5-monoiodinases that convert T4 to T3, and decreased delivery of T4 substrate for conversion to T3. Peeters et al. [16] provided evidence in support of the first mechanism with studies showing reduced tissue expression and activity of type 1 and 2 monodeiodinases (5-monoiodinases that convert T4 to T3) in liver and skeletal muscle biopsies obtained from ICU patients within minutes after death. Their results also showed increased tissue expression and activity of 5-monoiodinase activity (causing increased conversion of T4 to rT3) in the critically ill patients. There is also evidence to suggest that decreased thyroxine transport over the cell membrane may play a role in lowered T3 production in ill newborns.

### **7.6 Hyperthyroidism in the newborn**

Rarely, a newborn may have hyperthyroidism, or neonatal Graves' disease. This condition usually occurs if the mother has Graves' disease during pregnancy or has been treated for it before pregnancy. In Graves' disease, the mother's body produces antibodies that stimulate the thyroid gland to produce increased amounts of thyroid hormone. These antibodies cross the placenta and similarly affect the fetus. An affected newborn has a high metabolic rate, with rapid heart rate and breathing, irritability, and excessive appetite with poor weight gain. The newborn, like the mother, may have bulging eyes (exophthalmos). If the newborn has an enlarged thyroid gland (goiter), the gland may press against the windpipe and interfere with breathing at birth. A very rapid heart rate can lead to heart failure. Graves' disease is potentially fatal if not recognized and treated by a pediatric endocrinologist. Doctors suspect hyperthyroidism based on the typical symptoms and confirm the diagnosis by detecting elevated levels of thyroid hormone and thyroid-stimulating antibodies from the mother in the newborn's blood. The results of a screening test of thyroid function done in all newborns may reveal hyperthyroidism. Newborns with hyperthyroidism are treated with drugs, such as propylthiouracil, that slow the production of thyroid hormone by the thyroid gland. This treatment is needed only for a few months because the antibodies that cross the placenta from the mother eventually disappear from the infant's bloodstream.

### **7.7 Thyroid function in term and preterm infants in relation to neonatal illness and medication**

Many abnormalities along the pituitary-thyroid axis have been observed in critical illness associated with sepsis, myocardial infarction, cardiopulmonary bypass, and surgery. Such

abnormalities include an attenuated response of thyroid stimulating hormone (TSH) to thyrotropin releasing hormone (TRH), decreased pulsatile TSH release, and decreased serum thyroid hormone levels. In mild illness, decreased serum total and free triiodothyronine (T<sub>3</sub>) are the predominant abnormalities. However, as the duration and severity of illness increase beyond 3–5 days, decreased serum total and free thyroxine (T<sub>4</sub>) levels are also observed. Decreased circulating levels of thyroidbinding globulin (TBG), decreased serum binding of T<sub>4</sub>, and decreased 5-monoiodinase activity, (the enzyme that converts T<sub>4</sub> to T<sub>3</sub>) are also important contributing factors for the low thyroid hormone state of critical illness. It is not known how immaturity and disease influence postnatal thyroid function in infants <30 wk of gestational age. It is important to investigate the influences of disease and gestational age on the time course of thyroid hormones. Transient hypothyroxinemia is common in extremely premature infants, but has not been extensively investigated in ill term and preterm infants. Free thyroxine (FT<sub>4</sub>) levels in term and late preterm infants with respiratory distress would be inversely related to severity of illness. Further research is warranted to determine whether T<sub>4</sub> supplementation would be beneficial in term and late preterm infants with respiratory distress. (Paul DA et al. 1998; Paul DA et al 2010, Judy L et al. 2009, Simpson 2005, Williams 2005)

### **7.8 Thyroid dysfunction related to congenital cardiac defects**

Congenital heart disease is the most common form of congenital defect at birth. There are evidences that exists a very narrow relation between the thyroid gland and the heart during fetal development. Thyroid hormones are necessary for the functioning of the heart in the fetal and postnatal life. Cardiopulmonary bypass induces marked and persistent depression of circulating thyroid hormones in infants, possibly contributing to postoperative morbidity (cardiac low output, ventricular left dysfunction, vascular increased resistance and respiratory difficulty...) The aims to prevent thyroid dysfunction in affected newborns are to improve heart hemodynamics, vascular resistance and metabolism during the neonatal period and the prevention of long-term disabilities in the neurodevelopment of these newborns. Based on previous studies available, it appears that L-T<sub>4</sub> replacement should be considered in patients with hypothyroidism in presence of cardiac defects in the attempt to reverse these negative prognostic factors and improve the cardiovascular function ( del Cerro 2000, Mainwaring RD et al. 2001, Mainwaring RD et al. 2002, Klemperer JD 2002, Portman MA et al. 2004, Holzer R et al. 2004, Lynch BA et al. 2004, Fazio S et al. 2004, Dimmick S et al. 2004)

## **8. Conclusion**

Neonates and especially preterm infants are a very important population at risk of suffering the consequences of thyroid dysfunction. Alterations of thyroid function in premature infants, leading to low circulating levels of T<sub>4</sub> or T<sub>3</sub>, have been associated with impairment of neural maturation, as measured by nerve conduction velocity and by lower scores in the Bayley mental and motor scales (De Vries et al., 1996; den Ouden AL et al., 1996; Lucas A et al., 1988; Meijer WJ et al., 1992; Lucas A et al., 1996; Reuss ML et al., 1996). Iodine deficiency and excess may well be frequent causes of inadequate thyroid hormone levels and should be avoided. Such a close follow-up becomes mandatory if an iodine overload cannot be prevented. Premature infants in many countries are now in a situation of iodine deficiency,

precisely at a stage of development that is very sensitive to alterations of thyroid function. The recommended intake of iodine for preterm infants based on balance studies is 30  $\mu\text{g}/\text{kg}/\text{day}$ . Enteral and parenteral nutritional fluids are the principal sources of iodine intake in these infants. The volume of food ingested by the infant is small, iodine content in formula preparations is insufficient, parenteral nutrition does not supply enough iodine. Pregnant and lactating women and neonates are the main targets of the effects of iodine deficiency because of the impact of maternal, fetal and neonatal hypothyroxinemia on brain development of the progeny (Morreale de Escobar G et al., 2004; Lavado-Autric R et al., 2003; Morreale de Escobar G et al., 1998; Morreale de Escobar G et al., 2000). The neurological damage is clearly preventable if pregnant mothers are tested for thyroid function during the first trimester and by giving pregnant women, or even before pregnancy, sufficient iodine to avoid hypothyroxinemia. If the mother has adequate iodine nutrition, breast milk is the best source of iodine for the newborn. However, based on data from the literature and on metabolic considerations, it is proposed that the recommended dietary intake of iodine is 250-300  $\mu\text{g}/\text{day}$  for pregnant women, 225-350  $\mu\text{g}/\text{day}$  for lactating women, and 90  $\mu\text{g}/\text{day}$  for neonates and young infants (Zimmermann M et al., 2004). This problem is not exclusive to Spanish premature babies as the iodine content of many formulas in other countries is also inadequate. Therefore, supplements should be added if iodine intake is found to be inadequate. Breast milk appears to be the best source of iodine for the premature infant (Ares S et al., 1994; Ares S et al., 1995; Ares S et al., 1997; Ibrahim M et al., 2003, Zimmermann 2010). Prevention of iodine deficiency and follow-up is recognized as a priority. The number of extremely low birth weight infants is high. Correction of their iodine deficiency and thyroid dysfunction and their consequences appears, at present, to be an intervention with promising possibilities (Ares S et al., 1995; van Wassenaer AG et al., 1997; Vanhole C et al., 1997; La Gamma EF et al., 2006). However, too little is yet known of the different factors involved in the metabolism of iodine and thyroid hormones during late fetal life and their adjustment to the conditions faced by newborn infants to be able to standardize possible treatment protocols. Future research would be facilitated if newborn infants and preterm babies were followed during their stay in intensive care units with respect to their iodine nutrition and thyroid function ( $T_4$ ,  $FT_4$ ,  $T_3$ , TSH, thyroid binding globulin TBG, Tg) as carefully as they are followed for other organ functions (Morreale de Escobar G et al., 1998; Rapaport R, 2002; Ares S et al., 2007) (Figure 3)

The high prevalence of thyroid function alterations that demanded treatment and delayed TSH elevation in premature infants and in term newborns reinforce the need for a specific protocol, based on retesting procedures, for neonatal screening. In conclusion, in view of more reliable recent information on thyroid function and physiology of newborn infants, the iodine content of many formulas for feeding infants appears to be inadequate. Most ill newborns and premature babies do not ingest the amount of iodine recommended from 1992 by the ICCIDD, the WHO, and the European Community (Delange F, 2001; Delange F, 2004; WHO, UNICEF, ICCIDD, 2001). Producers of such formulas should be urged to comply with the new recommendations and to control that their products do so irrespective of the country where they are being used. This review focuses on neonatal transient hypothyroxinaemia, a condition characterized by temporary postnatal reductions in concentrations of Total  $T_4$  or Free  $T_4$ , with normal or low concentrations of thyroid stimulating hormone (TSH). There is neither an agreed quantitative definition, nor an agreed mode of measurement for the condition. Transient hypothyroxinaemia is not routinely

monitored yet it is thought to affect about 50% of preterm infants; it was thought to be without long-term sequelae but observational studies indicate that neurodevelopment may be compromised. The aetiology of transient hypothyroxinaemia is complex. There are significant contributions from the withdrawal of maternal-placental thyroxine transfer, hypothalamic-pituitary-thyroid immaturity, developmental constraints on the synthesis and peripheral metabolism of iodothyronines and iodine deficiency. It is not possible to distinguish clinically, or from laboratory measurements, whether transient hypothyroxinaemia is an independent condition or simply a consequence of non-thyroidal illness and/or drug usage. An answer to this question is important because studies of thyroid hormone replacement have been instigated, with mixed results.

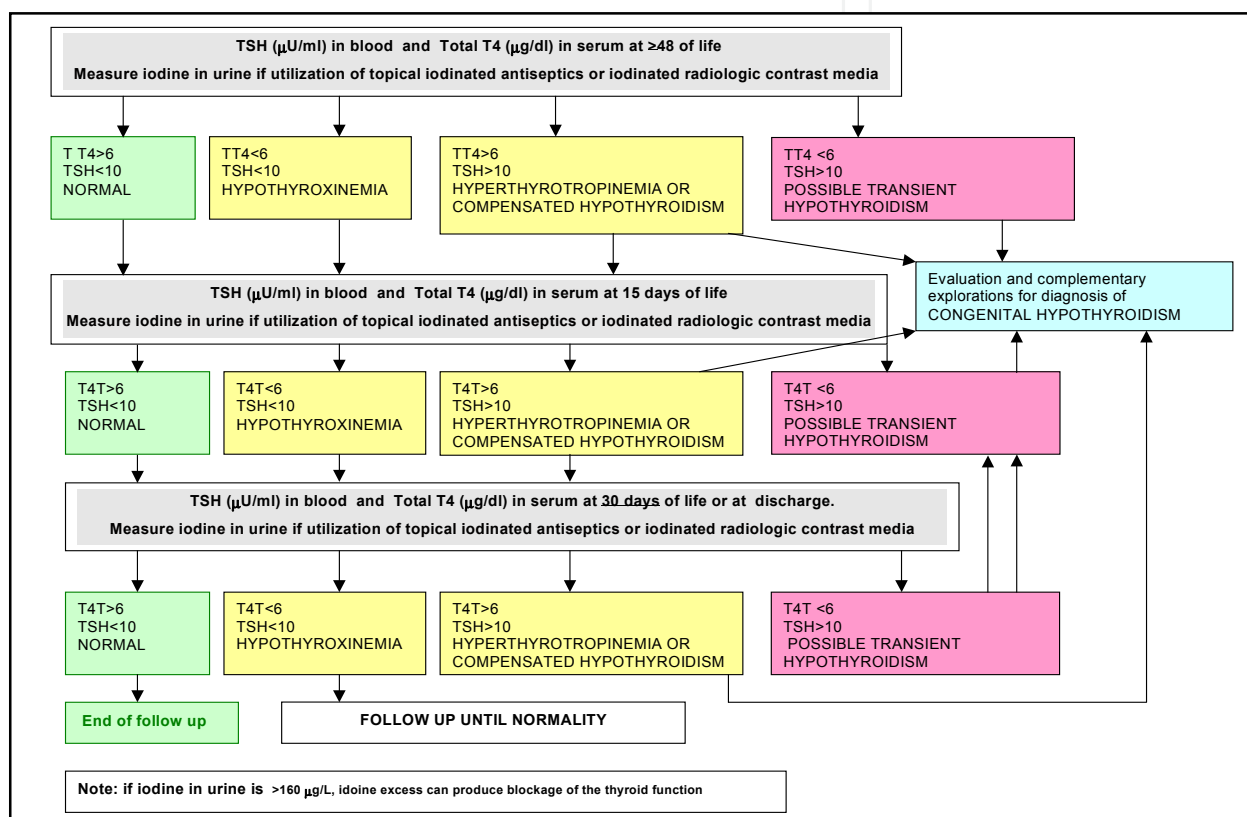


Fig. 3. Proposed protocol for monitoring neonatal thyroid function in special circumstances.

Until the aetiology of transient hypothyroxinaemia is better understood it would seem prudent not to routinely supplement preterm infants with thyroid hormones. Iodine deficiency, non-thyroidal illness and drug usage are the most modifiable risk factors for transient hypothyroxinaemia and are the clear choices for attempts at reducing its incidence. The high prevalence of thyroid function alterations that demanded treatment (1:242) and delayed TSH elevation in premature infants reinforce the need for a specific protocol, based on retesting procedures, for neonatal screening. The purpose of the present protocol is to systematically include the determination of T4 in blood spotted on DBS paper, in order to detect hypothyroxinemia, elevation of TSH, and other alterations in thyroid function and to establish the necessity to incorporate a routine into the Neonatal Thyroid Screening Program that would obtain a special screening specimen in infants at high risk of suffering alterations of their thyroid function (Table 3).

- An adequate iodine intake should be ensured in newborn infants.
- Enteral and parenteral nutrition fluids are the principal sources of iodine intake in these infants.
- If the mother has adequate iodine nutrition breast milk is the best source of iodine for the newborn. The volume of food ingested by the infant is low. The iodine content in formula preparations must be taken into account. Parenteral nutrition does not supply the preterm newborn with enough iodine to meet the recommendations. Supplements should be added if iodine intake is found to be inadequate. Most of the preterm babies are at high risk of iodine deficiency. Neonates and especially preterm infants are a very important population at risk of suffering the consequences of both iodine deficiency and excess, because of the impact of neonatal hypothyroxinemia on brain development.
- Iodine deficiency and excess ought to be avoided.
- Correction of their hypothyroxinemia, and its consequences appears, at present, to be an intervention with promising possibilities. Prevention and Follow-up in Pediatrics is recognized as a priority. The number of extremely low birth weight babies (ELBW) is increasing.
- Future research would be facilitated if: very premature infants are tested for thyroid function (T4, Free T4, T3, TSH, TBG, Tg) immediately after birth and repeatedly during their stay in intensive care units, and as carefully as they are followed for other organ functions. All babies with a TSH > 10 mU/l should be commenced on thyroxine at a dose of 10-15 micrograms/kg/day. Arrange to inform the family of the results on the same day and make arrangements to start thyroxine if necessary.
- Early treatment with thyroxine (before 10 - 21 days of age) is crucial if neurological disability is to be avoided.
- Treatment should be started as soon as diagnosis is confirmed (preferably the same day) following discussion with the endocrine team. Do not delay treatment if a member of the endocrine team cannot be contacted.
- If the laboratory TSH is between 4 and 10, please discuss with endocrine team.

Table 3. Summary and key points.

List of Abbreviations:

- ICCIDD: International Council for Control of Iodine Deficiency Disorders
- thyroxine (T4)
- 3,5,3'-triiodothyronine (T3)
- thyroglobulin (Tg)
- thyroid stimulating hormone (TSH)
- thyroid binding globulin (TBG)
- gestational age in weeks (GA)
- body weight (BW)
- Transient hypothyroxinaemia of prematurity (THOP)
- cerebral palsy (CP)
- ELGAN—extremely low gestational age neonate

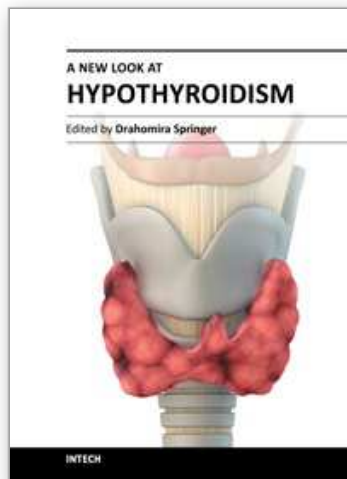
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## **A New Look at Hypothyroidism**

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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