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# Iodine Balance, Iatrogenic Excess, and Thyroid Dysfunction in Premature Newborns

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**Iodine is a trace element that is essential for the synthesis of thyroid hormones. The thyroid hormones, thyroxine and 3,5,3′-triiodothyronine, are necessary for adequate growth and development throughout fetal and extrauterine life. 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 is different depending on age groups. The iodine intake required is at least 15 μg/kg/d in full-term infants and 30 μg/kg/d in preterms. 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.**


**KEYWORDS** iodine intake, hypothyroidism, pregnancy, breast milk, thyroid hormone

Iodine is a trace element which is a prerequisite for the synthesis of thyroid hormones. These hormones, thyroxine ($T_4$) and 3′,3,5,-triiodothyronine ($T_3$), are necessary for adequate growth and development throughout fetal and extrauterine life. These hormones regulate many metabolic processes, as follows: somatic growth; cardiac, pulmonary, and bone maturation; central nervous system maturation; oxygen consumption; protein, lipids, and carbohydrates metabolism; surfactant synthesis; and lung maturation.[1-3] Brain and lung maturation have received special attention, because of the potentially irreversible or life-threatening consequences associated with early thyroid hormone deficiency.[3-8] Mild/moderate iodine deficiency during pregnancy and/or 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 neonatal life. 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 close involvement between human brain development and thyroid hormones is widely accepted.[9] The effects of $T_3$ 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 prenatal 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 $T_4$ 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.[3,5,7,8,10,11]

The incidence of permanent congenital hypothyroidism in preterm newborns is not higher than in children at term, but the frequency of hypothyroxinemia and transitory hypothyroidism is high during the neonatal period. There are several causes for alterations of thyroid function, as follows: incomplete maturation of the hypothalamic-pituitary-thyroid axis, interruption of maternal transfer of thyroid hormones to the fetus across the placenta, changes in thyroid function that accompany severe illness, and the effect of neonatal medication (dopamine, heparin, corticoids, etc.). Quite prominent

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doi:10.1053/j.semperi.2008.09.006

**Table 1** Iodine Recommended Daily Requirements (RDA)

| Group | Age | Iodine RDA |
|---|---|---|
| Preterm infants | 0 to 5 months | >30 μg/kg/d |
| Term infants | | 15 μg/kg/d |
| Children | 6 to 12 months | 90 μg/d |
| | 1 to 3 years | 90 μg/d |
| | 4 to 6 years | 90 μg/d |
| | 7 to 10 years | 120 μg/d |
| Adults | | 150 μg/d |
| Pregnant women | | 230 μg/d |
| Lactating women | | 260 μg/d |
| Pregnant and lactating women* | | 250 to 300 μg/d |

*Recent ICCIDD RDAS.

are iodine deficiency during the perinatal period. 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 for different age groups is summarized in Table 1.[12,13] To meet such requirements, the iodine content of formulas for premature newborns should contain 20 μg/dL, and that of first and follow-up preparations should contain 10 μg/dL. We refer here to these new recommendations as those of the International Council for the Control of Iodine Deficiency Disorders.[12-16] The exposure to an iodine excess during the neonatal life, caused by iodine-containing antiseptics and radiologic contrast media, may impair thyroid function during a period of development when thyroid hormones are very important for the brain.[9,17]

## Thyroid Function in the Fetus and Newborn

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.[9,18-20] 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. It is often presumed that the low thyroxine levels in premature infants are a continuation of levels experienced *in utero*, a condition referred to as transient hypotiroxinemia of prematurity, but data derived from blood obtained by cordocentesis[21] have shown that thyroid stimulating hormone (TSH) and $T_4$ levels sampled from fetuses are higher than those found in premature infants of the same gestational age. Hypothyroxinemia of prematurity is thought to be caused by several factors. These include the incomplete maturation of the hypothalamic-pituitary-thyroid axis and relative immaturity of the type I iodothyronine deoidinase enzyme systems, the untimely interruption of maternal transfer of thyroid hormones to the fetus across the human placenta, maternal antibodies, postnatal drugs (dopamine, heparin, corticoids, etc.), and disease.[22] The percentage contribution of iodine deficiency to hypothyroxinemia may be greater in the more immature infants who have a very low iodine supply: Serum $FT_4$, $T_3$, thyroglobulin (Tg), and TSH of preterm neonates were affected negatively, independently from age, by a low iodine intake.[22-25] Iodine deficiency contributes to about 30% of the hypothyroxinemia in enterally and parenterally fed preterm infants of 27 to 30 weeks gestation.

## Iodine Requirements

The availability of iodine during the peri- and postnatal period of development should both ensure the minimal requirements and not exceed the minimum amounts blocking their thyroid function. The recommended intake of iodine in neonates reflects the observed mean iodine intake of young infants exclusively fed human milk in adequate iodine intake 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.[12,14-16,24,26,27] The iodine requirement in neonates was evaluated from metabolic studies by determining the values that resulted in a situation of positive iodine balance, which is required to insure a progressively increasing intrathyroidal iodine pool in the growing young infant.[14] The intake required to achieve a positive iodine balance is at least 15 μg/kg/d in full terms and 30 μg/kg/d in preterms.[12] To reach adequate intake, the iodine content of formulas for premature newborns should contain 20 μg/dL; that of all other preparations should contain 10 μg/dL.[28,29] In our unit we studied thyroid gland volume by ultrasound and found that the volume varied from 0.3 to 1.3 mL in preterm infants during the first month of life and 0.9 mL in term infants at birth.[30]

## Iodine Content of Human Milk and Newborn Iodine Intake

We followed up a cohort study on thyroid function, iodine intake, and excretion of 67 premature infants born before 30 weeks of gestation. The average iodine concentration in the milk of the mothers was 13.7 ± 1.9 μ/100 mL (range, 4.5-48). No statistically significant differences were found between samples of women at different gestational ages or between different times during the lactation period. Mean values for the iodine content of breast milk are quite variable. The iodine intake is lower than the recommendations in most groups of prematures on formulas alone. The premature babies do not ingest the 150 to 200 mL/kg/d recommended for term babies until they are approximately 1 month old and weigh 2 kg. Because of the small volume of milk ingested, the iodine intake of the newborns was <30 μg/kg per day (Table 2). Infants on current standard regimens of total parenteral nutrition have a mean iodine intake of 3 μg/kg/d. The manufacturer's recommended dosage for infants is 1 mL/kg/d of Peditrace parenteral solution, which contains 1.3 μg/mL potassium iodide equivalent to 1 μg iodide/kg/d. Infants on total parenteral nutrition have a mean iodine intake of only 3

**Table 2** Iodine Intake during the First Month of Life in Babies Born at <30 Weeks

| | 1st Sample | 2nd Sample | 3rd Sample | 4th Sample |
|---|---|---|---|---|
| Number of babies | 54 | 55 | 52 | 49 |
| Age in days | 0.3 ± 0.0 | 9.1 ± 0.5 | 18.5 ± 0.7 | 28.4 ± 1.0 |
| Gestational age (wk) | 27.0 ± 0.25 | 28.9 ± 0.2 | 30.3 ± 0.2 | 31.8 ± 0.27 |
| Weight (g) | 987.0 ± 30.9 | 938.7 ± 30.0 | 1035.9 ± 34.4 | 1221.5 ± 50.3 |
| Volume of formula (ml) | 0 | 61.8 ± 8.4 | 113.1 ± 11.0 | 161.4 ± 12.5 |
| Iodine intake (μg I/d) | 0.2 ± 0.1 | 13.8 ± 3.0 | 23.5 ± 3.1 | 23.6 ± 2.0 |

μg/kg/d. With this intake, preterm babies on parenteral nutrition are at high risk of iodine deficiency.[31,32]

## Iodine Excretion into the Urine and Iodine Balance

During the first weeks of life, it was observed that the 27- to 33-week postmenstrual age sick infants excreted approximately 1.5 times the amount of iodine into the urine than healthy term babies, despite their lower iodine intake. The urinary iodine excretion was calculated from the volume and the iodine concentration of the 24-hour urine sample. The mean iodine excretion in urine was 103.2 ± 6.5 μg I/L. The daily iodine balance was calculated as the difference between the iodine intake and the iodine excretion. This negative balance is greater the more immature the preterm infant. This condition is transient, with the balance changing from negative to positive with increasing age (Fig. 1). This finding suggests that the premature infants in negative balance are unable to "retain" all the iodine they are ingesting, and that an increased intake would not correct their negative iodine balance (Table 3). Most of the 31- to 36-week gestational age healthy preterms and term infants were in positive iodine balance, which increased with the iodine intake and, to a lesser degree, with postmenstrual age, retaining 80 to 90% of the iodine intake, and the iodine excretion in urine was lower than the intake.[23]

## 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).[33-42] The most frequently identified sources of excess iodine leading to problems in neonates result from the use of iodine-containing disinfectants (10,000 μg 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 $T_4$ and $T_3$, 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. There is a marked individual variability in the sensitivity to iodine-overload. Urinary iodine concentrations above 16 μg/dL,[43] 20 μg/dL,[44] and 25 μg/dL[22] may impair thyroid function in neonates. Some iodinated contrast agents, such as ipodate and iopanoic acid, are well-known inhibitors of all known iodothyronine deio-

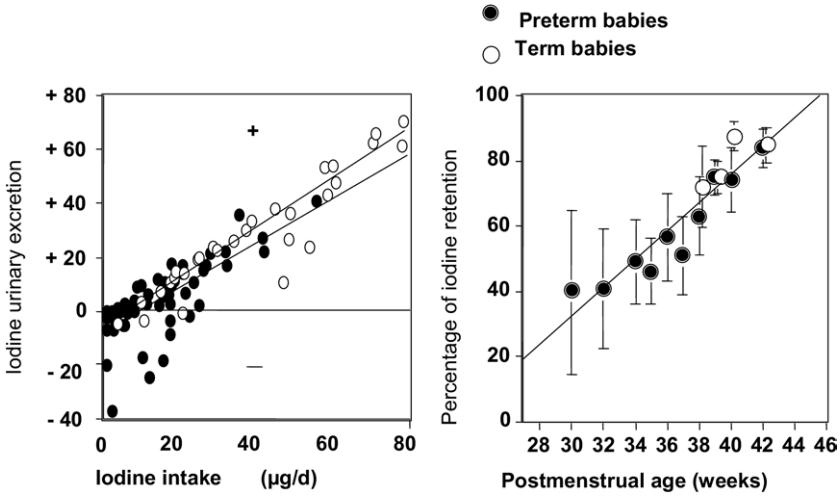


**Figure 1** Left panel: Individual Iodine intake of preterm (31-36 weeks of gestation) and term newborns (μg/day) at different postnatal ages in days. Right panel: Mean (±SEM) percentage of iodine retention of preterm (31-36 weeks of gestation) and term newborns (μg/day) at different postmenstrual ages in weeks.

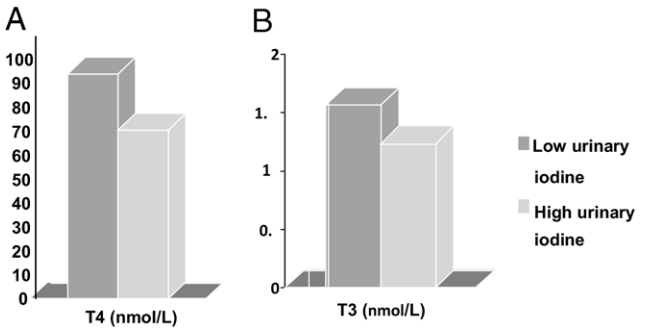


**Figure 2** Mean total $T_4$ (A) and $T_3$ (B) serum concentration in preterm babies related to low or high iodine urinary excretion. Effect of iodine excess in the neonatal period.

dinases, including the type II 5′-deiodinase, which is responsible for the local production of $T_3$ from $T_4$ in the developing mammalian brain.[45] The use in newborn infants might be especially dangerous, because of the sensitivity of the developing brain to low intracerebral $T_3$ levels. A nutritional state of iodine deficiency also increases the risk of hypothyroidism and alterations of thyroid function in neonates as a result of iodine-overload. Premature babies are at a higher risk of complications than term newborns, possibly due to multiple factors that can affect thyroid function and elevate the risk of blockage of the thyroid gland: immaturity of thyroidal autoregulatory mechanisms, iodine-deficiency resulting from an inadequate nutritional supply of this element during gestation and during the neonatal period, severe neonatal diseases, medications that can affect thyroid function. Guidelines for neonatal thyroid screening often take into account the special problems posed by premature infants. Some programs stress that samples be taken for thyroid function tests not only on the date after birth when they are routinely taken in term neonates, but also at later ages, especially if contrast media or radiological examinations have been performed. Determination of at least serum $T_4$ and TSH, and urinary iodine, appear to be a very good marker to detect impairment of thyroid function due to iodine overload. Thus, frequent monitoring of thyroid status is strongly recommended whenever premature babies are submitted to iodinated compounds. This adverse complication should be brought to the attention of neonatologists: even a relatively minor iodine-overload may impair thyroid function during a period of development when thyroid hormones are very important for the brain. The prompt early diagnosis and treatment of the alterations of thyroid function associated with iodine excess could have beneficial effects in the prevention of developmental abnormalities. The risk of transient hypothyroidism may be avoided by the use of iodine-free compounds. Chlorhexidine should be used for skin disinfection and surgery.[22,32,46]

## Iodine Deficiency and Excess Related to Thyroid Function

$T_4$, $FT_4$, and $T_3$ levels are lower in preterm neonates as compared with term newborns, increasing progressively with maturation, whereas TSH levels are the same. The iodine intake does affect the circulating levels of $FT_4$, $T_3$, Tg, and TSH in preterm infants, independently of their age. Serum $FT_4$, $T_3$, Tg, and TSH of preterm neonates were affected negatively, independently of age, by a low iodine intake. The percentage contribution of iodine deficiency to hypothyroxinemia may be greater in the more immature infants who have a very low iodine supply: serum $FT_4$, $T_3$, Tg, and TSH of preterm neonates were affected negatively, independently from age, by a low iodine intake.[31] We studied the possible relationship between circulating parameters of thyroid function and their high iodine excretion. These babies had lower serum $T_4$ ($70.4 \pm 6.4$ nmol/L) than ($93.9 \pm 5.4$ nmol/L) babies with an iodine excretion in normal ranges during the 15 to 30 days of life ($P < 0.04$). Those babies with high iodine excretion had lower serum $T_3$ ($1.23 \pm 0.0$ nmol/L) than ($1.56 \pm 0.1$ nmol/L) babies with iodine excretion in normal ranges during the first 7 to 30 days of life ($P < 0.008$) (Fig. 2).

## Discussion

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 as measured by nerve conduction velocity and by lower scores in the Bayley mental and motor scales.[5-8,12,18] Iodine deficiency and excess may well be frequent causes of inadequate thyroid hormone levels and should be avoided. Enteral and parenteral nutrition fluids are the principal sources of iodine intake in newborn infants. The volume of food ingested by the infant is low, and most of the iodine content in formula preparations is insufficient. Parenteral nutrition does not supply the premature neonate with enough iodine; therefore, supplements should be added if iodine intake is found to be inadequate.[47]

Prevention in pediatrics is recognized as a priority. The

**Table 3** Percentage of Preterm and Term Neonates in Negative Iodine Balance*

| Group by GA (wk) | 27 to 30 | 31 to 33 | 31 to 33 | 34 to 36 | 34 to 36 | Term |
|---|---|---|---|---|---|---|
| Postnatal age | | Sick | Healthy | Sick | Healthy | |
| 5 days | 75% | 28% | 11% | 21% | 11% | 7% |
| 15 days | 33% | 14% | 0% | 0% | 0% | 0% |
| 30 days | 0% | 0% | 0% | 0% | 0% | 0% |

*Calculated using as 100% the number of infants in each group with complete 24-hour urine excretion data.

number of extremely low birth weight babies is high. Breast milk appears to be the best source of iodine for the premature infant.[47] Prevention of iodine deficiency and follow-up is recognized as a priority. Correction of their iodine deficiency and hypothyroxinemia and its consequences appears to be an intervention with promising possibilities.[48-50] 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 extremely low birth weight infants to be able to standardize possible treatment protocols.[51] Future research would be facilitated if 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.[19,32] 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.

## Acknowledgments

We are grateful for grants from the Fondo de Investigaciones Sanitarias (Grant 99/371 to S.A. and PI03/1417 to G.M.E.) and the Instituto de Salud Carlos III, RCMN (03/08) for financial support.

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