

# A negative iodine balance is found in healthy neonates compared with neonates with thyroid agenesis

B Bakker<sup>1</sup>, T Vulsma<sup>1</sup>, J de Randamie<sup>1</sup>, A M Achterhuis<sup>1</sup>,  
B Wiedijk<sup>1</sup>, H Oosting<sup>2</sup>, C Glas<sup>3</sup> and J J M de Vijlder<sup>1</sup>

<sup>1</sup>Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Division of Pediatric Endocrinology, Amsterdam, The Netherlands

<sup>2</sup>Department of Clinical Epidemiology and Biostatistics, Academic Medical Center, Amsterdam, The Netherlands

<sup>3</sup>Friesland Nutrition – FDF, Leeuwarden, The Netherlands

(Requests for offprints should be addressed to B Bakker, Academic Medical Center, University of Amsterdam, Emma Children's Hospital AMC, Division of Pediatric Endocrinology, P.O. Box 22700, 1100 DE Amsterdam, The Netherlands)

## Abstract

We studied the effects of the presence or absence of the thyroid gland on the iodine metabolism and excretion in term Dutch newborns by performing a retrospective study of the urinary iodine excretion in 193 term newborns with abnormal congenital hypothyroidism screening results. Thirty-six euthyroid newborns with decreased thyroxine-binding globulin levels were compared with 157 hypothyroid patients, 54 due to thyroid agenesis and 103 due to thyroid dysgenesis. A significant difference in the urinary iodine excretion was observed between the agenesis group (mean: 28 µg/24 h) and the euthyroid newborns (mean: 46 µg/24 h,  $P=0.001$ ).

In conclusion, healthy, euthyroid, term newborns excreted more iodine in their urine than newborns with thyroid agenesis. These results strongly indicated the existence of a temporarily negative iodine balance: the excretion of iodine prevailed over the intake and the newborn's thyroidal iodine, stored during pregnancy, could be used for thyroxine synthesis in the postnatal period. Since healthy term neonates were able to maintain adequate plasma free thyroxine concentrations under normal TSH stimulation, the prenatally acquired iodine stores could be considered sufficiently high to compensate for the transient postnatal losses.

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## Introduction

An insufficient supply of the scarce but essential micro-nutrient iodine, an integral part of thyroid hormone, results in impaired thyroxine ( $T_4$ ) production. Iodine deficiency is a current health risk for roughly one-fifth of the earth's population, and is especially a threatening condition for normal brain development during the period from early pregnancy to infancy. Measurement of urinary iodine excretion is considered to be a reliable indicator of iodine status (Recommended Daily Allowances 1989). In the steady-state condition in adults there is a close relationship between intake and excretion of iodine.

There are marked regional differences in urinary iodine excretion and, hence, in dietary iodine intake throughout Europe (Delange 1996b). In The Netherlands, potassium iodide is added to bread and table salt. Groups consuming little bread or unsalted bread such as female adolescents and elderly people are reported to have borderline urinary iodine excretions (Van Rees-Wortelboer *et al.* 1987) and develop goitre related to iodine deficiency (Brug *et al.* 1992). Pregnant women on a salt-restricted diet (and consequently their newborns) are also at risk. Within a

population, newborns are one of the groups vulnerable to iodine deficiency; a shortage of  $T_4$  will impair normal central nervous system development. The exact iodine intake in newborns is almost impossible to measure. The iodine supply at large is considered to be sufficient when the vulnerable groups in a population also attain a sufficient dietary intake. In The Netherlands little research has been done regarding urinary iodine excretion in healthy newborns and those with congenital hypothyroidism (Gons *et al.* 1985, Delange & Bürgi 1989).

Our main aim was to investigate whether the neonatal supply of iodine in The Netherlands is sufficient or marginal as in certain groups of Dutch adults. Investigation of iodine excretion in newborns with different aetiological categories of congenital hypothyroidism (CH) may provide an insight into the supply and metabolism of iodine in this age group. The 24-h urinary iodine excretion data of term Dutch newborns referred to paediatricians because of aberrant CH screening results were analysed retrospectively. We focused on differences in urinary iodine excretion between newborns with thyroid agenesis where there is no buffer compartment for iodine, or with thyroid dysgenesis where there is restricted potential for

accumulating iodine and newborns with decreased thyroxine-binding globulin (TBG) concentrations where there is completely normal thyroid hormone status. The data allowed us to make some suggestions about the iodine pool in the thyroid gland.

## Patients and Methods

### Patients

All the neonates that were studied were born between 1983 and 1996 and were referred to their local paediatrician because of aberrant CH screening results. As part of the aetiologic classification procedure, Dutch paediatricians are advised to collect 24-h urine specimens for the determination of total iodine excretion (Gons *et al.* 1983). Urine samples were collected at a mean age of 23 days and the collections were nationwide. We excluded those patients with a history of pre- or postnatal exposure to excessive amounts of iodine, those with thyroid dys-hormonogenesis, preterm infants (gestational age <37 weeks), and those with incomplete data (less than a 24-h collection period, where data on gestational age were missing and where there was uncertainty about the aetiology). In this way we obtained a total of 193 patients (111 girls and 82 boys): 36 with decreased TBG concentrations, 54 with thyroid agenesis and 103 with thyroid dysgenesis. Twenty-four-hour collections were mostly done before the initiation of T<sub>4</sub> therapy. In more recent years it has become clear that T<sub>4</sub> therapy should never be delayed because of the diagnostic process. This means that in the 1990s T<sub>4</sub> therapy might have been started in some patients whilst the 24-h urine collection was being made; see also the Discussion.

### Methods

In The Netherlands, the screening method for CH is primarily performed as T<sub>4</sub> screening, with additional thyrotrophin (TSH) determinations in the 20% of samples with the lowest T<sub>4</sub> concentrations. The advantage of the T<sub>4</sub> screening programme, to which in 1995 a TBG determination was added, is the detection of secondary and tertiary hypothyroidism. Depending on the levels of total T<sub>4</sub>, TSH and the T<sub>4</sub>/TBG ratio a child is either referred to a paediatrician directly or a second heel puncture is done.

We received frozen 50–100 ml specimens of 24-h urine collections. After destruction with chloric acid, the iodine concentration was measured in urine, milk and formula by the cerium-arsenite method (de Vijlder *et al.* 1978), using a Cobas Fara spectrophotometer (Hoffmann-la Roche Ltd, Basel, Switzerland). The detection level of the assay is 5 µg/l, intra- and interassay coefficients of variation are at most 3.7 and 3.3% respectively.

### Aetiologic classification

The euthyroid group consisted of healthy children with normal plasma free thyroxine (FT<sub>4</sub>) and TSH concentrations and a decreased TBG concentration (TBG <380 nmol/l or 20 mg/l). Children with agenesis of the thyroid gland had, at the time of detection, very low but detectable FT<sub>4</sub> levels (reflecting the exponentially decreasing amounts of T<sub>4</sub> from maternal origin (Vulsma *et al.* 1989)), very high TSH concentrations and undetectable plasma thyroglobulin concentrations. On imaging studies (<sup>123</sup>I<sup>-</sup>, ultrasound) no thyroid tissue could be demonstrated in the neck/head region. Patients with a dysgenetic thyroid gland (characterised by a dystopic remnant at radioiodide imaging) had variable decreased plasma FT<sub>4</sub> and variable plasma thyroglobulin concentrations. The methods for aetiologic classification have been described in detail previously (de Vijlder & Vulsma 1996).

### Statistical analysis

To compare the mean urinary iodine excretions of the three groups, the Kruskal–Wallis test was used. When significant differences were found, the means were compared by the Mann–Whitney test. *P* Values were corrected by means of the Bonferroni method. The Mann–Whitney test was also used for comparison of urinary iodine excretion with respect to gender. The urine samples were collected over a long period (1983–1995). Cohorts of 1 year were created; one-way analysis of variance (ANOVA) was used for comparison of the values of these cohorts. One-way ANOVA was also used to check for differences between the day of collection and for differences in urinary iodine excretion in the 12 different provinces of The Netherlands. Analysis of covariance (BMDP statistical software, Cork Technology Park, Cork, Republic of Ireland) was applied for comparing the difference in urinary iodine excretion between groups with a correction for the day of collection, the latter being the covariate.

### Fluid balance

In order to make calculations on milk intake (breast milk or formula) and urine production we used the well-known relationship between caloric expenditure and water balance (Finberg *et al.* 1982). This approach gives the most accurate way of determining insensible water losses in neonates, giving us the ability to perform a control on the 24-h urine sampling. We accepted that the daily non-urinary water loss was 50 ml/kg per 24 h for euthyroid neonates (see Table 1), 45 ml/kg per 24 h as evaporation losses through skin and lungs and 5 ml/kg per 24 h as water loss via defaecation (McCance 1973, Finberg *et al.* 1982). The daily milk intake for the euthyroid newborns

**Table 1** Daily water volumes in insensible loss, milk intake and urinary output

Parameter	Euthyroid neonates (TBG deficiency)
	Daily non-urinary water
Average daily milk intake	175 ml/kg per 24 h*
Daily urinary production	125 ml/kg per 24 h
Mean stated 24-h urinary volume	301 ml/24 h
Mean calculated 24-h urinary volume (4 kg)	500 ml/24 h

\*Lower limit=150 ml/kg per day, upper limit=200 ml/kg per day.

at the age of 4 weeks post partum was assessed to be 150–200 ml/kg per 24 h. This results in an average water intake of 175 ml/kg per 24 h (McCance 1973) at this age. We calculated that the daily urinary production on the basis of a 4 kg body weight at the age of 3 weeks would be 500 ml/24 h (see Table 1). To check whether the 24-h urine samples were collected correctly, we made calculations on food intake and 24-h urinary excretion at the time of collection, using the above-mentioned relationship between caloric expenditure and water balance.

With a determined mean iodine content in breast milk of 103 µg/l (95% confidence interval (CI): 83–123) and of 124 µg/l (95% CI: 119–128) in formula (this study, see Results), we calculated the mean daily iodine intake. With an estimated weight of 4 kg at the age of 4 weeks, the euthyroid child drinks a total of 4 × 175 ml (see Table 1) =700 ml/day. This gives a mean daily iodine intake of 72 µg (95% CI: 58–86) for breast-fed newborns and 86 µg (95% CI: 83–90) for bottle-fed newborns. These amounts are higher than the mean measured excreted amount of 46 µg iodine (95% CI: 37–56) per day (see Table 2). Because most Dutch newborns are breast-fed we will focus on the calculations for breast-fed children. The mean 24-h urinary volume that we calculated was 500 ml and the mean 24-h volume that was stated was 301 ml (see Table 1). This 40% difference can be explained either by losses during urine collection and/or non-urinary iodine losses. The first possibility is most likely because a 24-h

collection of urine in plastic sample bags with an adhesive layer around the genitalia is a well-known troublesome procedure.

It is highly conceivable that this 40% loss in 24-h urine collection also applies to the thyroid agenesis and dysgenesis groups, meaning that the significant difference in 24-h urinary iodine excretion between the agenesis group and the euthyroid group remains.

## Results

The three groups together, with a total of 193 neonates with known aetiologies, had a mean urinary iodine excretion of 37 µg/24 h (Table 2). No significant differences in urinary iodine excretion between girls ( $n=111$ ) and boys ( $n=82$ ) were observed. The 24-h urine samples, collected from 1983 till 1996, were analysed in cohorts of 1 year and one-way ANOVA did not reveal any significant difference over these years ( $P=0.75$ ). No significant geographical differences are found in The Netherlands.

The euthyroid group had a mean iodine excretion of 46 µg/24 h and the thyroid agenesis group 28 µg/24 h (Table 2). This difference is statistically significant ( $P=0.001$  by the Mann–Whitney test), also after correction for the age at collection. The thyroid dysgenesis group had an in-between mean urinary iodine excretion of 38 µg/24 h. The euthyroid group as compared with the thyroid agenesis group not only had a higher iodine excretion per day (expressed in µg/24 h) but also in concentration (expressed in µg/l). A slight increase in urinary iodine excretion was observed when the collection time was at a later age (data not shown), probably related to the increasing daily volume of milk that the growing infant drinks. The euthyroid group was investigated later than the agenesis group (see Table 2) due to later referral. However, this increase in urinary iodine excretion because of a later collection time does not account for the difference found between the euthyroid and agenesis groups, as calculated by analysis of covariance.

A recent analysis in our laboratory of the food of Dutch neonates revealed a mean iodine concentration of 103 µg/l

**Table 2** Urinary iodine excretion in relation to the aetiological category in neonates referred because of an abnormal CH screening result

Diagnosis	Number of neonates (girls)	Mean age at collection (days)	Urinary iodine excretion in µg/24 h		Urinary iodine excretion in µg/l		Stated urine production (ml/24 h)	Mean birth weight (g)	Mean FT <sub>4</sub> level (pmol/l)
			Mean	95% CI	Mean	95% CI			
Euthyroid neonates	36 (6)	28	46*	37–56	150	127–172	301	3469	18.4
Agenesis	54 (32)	17	28*	22–33	121	104–139	241	3592	2.6
Dysgenesis	103 (73)	24	38	34–43	159	135–182	264	3543	7.5
All	193 (111)	23	37	34–39 33–40	148 147	137–159 132–161		3465	8.9

\*Statistically significant difference by Mann–Whitney test ( $P=0.001$ ).

in breast milk (95% CI: 83–123 µg/l) and 124 µg/l in formula (95% CI: 119–128 µg/l).

## Discussion

Thyroid hormone, and hence its unique and indispensable substrate iodine, is very important for cerebral development. Several studies concerning CH have shown that pre- and postnatal shortage of T<sub>4</sub> leads to impaired neurodevelopment (Porterfield & Hendrich 1993, Kooistra *et al.* 1994, Derksen-Lubsen & Verkerk 1996). Even more devastating for neurodevelopment is (severe) iodine deficiency, which impairs both maternal and foetal/infantile thyroid hormone synthesis (Delange 1996a).

During early pregnancy, the human foetus is completely dependent on the maternal thyroid hormone status, because the foetal thyroid gland secretes hardly any thyroid hormone before 16 weeks of gestation. From that age on foetal thyroid hormone production gradually increases, but the foetus remains completely dependent on the iodine supply by the mother. There are two sources of iodine for the foetus: (1) maternal (inorganic) iodide from alimentary sources, passing through the placenta and (2) maternal iodothyronines, deiodinated in the placenta. The mean amount of iodine stored in the foetal thyroid is dependent on the geographical iodine status; in decreased newborns from Toronto it was measured to be approximately 300 µg (*n*=13), stored in thyroid glands of about 1 g (Delange & Ermans 1996). Canadian newborns in this area excrete a mean of 148 µg iodine/l urine, nearly the same as that found for Dutch newborns (this study).

After birth the iodine supply changes from the placental to the enteral route. The postnatal sudden rise in plasma thyroid hormone concentrations follows an abrupt increase in TSH within the first few hours after birth. The prenatally stored iodine pool in the thyroid gland allows this sudden increase in thyroid hormone production. In addition to this, the iodine in the ingested milk is important for a continuing production of thyroid hormone. The amount of iodine in milk appears to be variable; we measured a mean of 103 µg/l in breast milk and 124 µg/l in formula. The prenatally stored pool of iodine in the thyroid gland cannot be measured in living neonates.

In order to evaluate the contribution of the prenatally stored thyroidal iodine in maintaining euthyroidism, we compared the urinary iodine excretion per day (and per litre) in newborns having a normal thyroid gland with children without any thyroid tissue. In this thyroid agenesis group the iodine excretion must reflect the postnatal iodine supply.

Urinary iodine excretion can be expressed in several ways: per litre (µg/l), per 24 h (µg/24 h) or per gram creatinine (µg/g creatinine), the latter being used when only portions of urine are being studied. The urinary creatinine concentration in our study group varied from

0.5 to 4.0 mmol/l. Given this large variation and also the reports by others that urinary iodine excretion/g creatinine is not a good measure for children (Furnée *et al.* 1994, Remer & Manz 1994) we chose to use urinary iodine excretion per 24 h in our study.

Gons *et al.* (1985) found in 151 Dutch newborns, with and without CH, a median value of 31 µg/24 h. The mean urinary iodine excretion of 37 µg/24 h in our study is somewhat higher, probably related to group differences. The iodine excretion is much higher than in Denmark (Nøhr *et al.* 1994), Germany (Peiker *et al.* 1989) or Spain (Ares *et al.* 1997).

In the population of newborns studied we found a significantly lower mean iodine excretion in the thyroid agenesis group than in the euthyroid group, both in amount per day (µg iodine/24 h) and per litre urine (µg iodine/l) (see Table 2). The 40% calculated loss within the 24-h urine collection (as outlined in the section on *Fluid balance*) does not affect the significant difference between the agenesis group and the euthyroid group. The fact that some of the more recently studied children might already be on T<sub>4</sub> supplementation while collecting 24-h urine samples only adds to the already significant difference in 24-h urinary iodine excretion between the agenesis group and the healthy TBG-deficient group. The agenesis newborns are more likely to have signs and symptoms of hypothyroidism, which incidentally may have led to T<sub>4</sub> administration during the 24-h urine collection.

Severely hypothyroid newborns compared with euthyroid children will drink less milk, giving a reduction in urinary iodine excretion. However, if the measured difference was exclusively caused by a reduction in milk intake, one would expect similar reductions in both iodine and water excretions and, as a consequence, equal iodine concentrations in the urine samples of both groups. Because this is not the case (see columns 4 and 6, Table 2) our data are indicative of a transient negative iodine balance (excretion exceeds intake) in the euthyroid newborns.

Another factor possibly contributing to the reduced urinary iodine excretion in the agenesis group might be caused by decreased iodine absorption from the intestinal tract in hypothyroid newborns; however, there are no conclusive data to support this (Vassilipoulou-Sellin & Sellin 1996).

The renal excretion of iodide shows a half-life of about 7 h (Bikker *et al.* 1996). As far as is known this is not significantly affected by thyroid hormone status. Even if the renal excretion was affected by hypothyroidism, this cannot account for a lower iodide excretion, since this would most likely be counteracted via an increase in the plasma iodide concentration.

The age at collection influences urinary iodine excretion. The mean day of collection for the agenesis group was 17 days post partum (95% CI: 16–19) and 28 days for the euthyroid group (95% CI: 23–33). By analysis of

covariance, we calculated that a difference in the time (day) of collection does not account for the differences in urinary iodine excretion between the groups.

Ares *et al.* (1997) have also described a temporary negative iodine balance during the first week of life in a small group of very premature newborns in Spain. The 24-h urinary iodine excretion in term Spanish newborns was very low (around 5 µg/24 h). Because the mean daily iodine intake in Spain is much lower than in The Netherlands (Delange & Bürgi 1989, Delange 1996b) it is to be expected that the amount of prenatally accumulated iodine will be lower.

In conclusion, this is the first report to show a negative iodine balance in healthy term newborns living in an iodine-sufficient area (The Netherlands). The extra amount of iodine excreted in the urine of these euthyroid newborns compared with thyroid agenesis patients has to originate from the major storage place of iodine: the thyroid. This negative iodine balance does not jeopardise T<sub>4</sub> production and reflects an adequate foetal iodine storage. Apparently the maternal iodine intake in The Netherlands covers the infant's thyroid hormone production during the first weeks of life. Ideally the external iodine supply should never be a rate-limiting factor in the synthesis of thyroid hormone. From our data we cannot exactly calculate the optimal daily iodine intake. In The Netherlands we seem to be on the safe side with the amounts of iodine in both breast milk and formula. In the first days after birth the negative iodine balance can be interpreted as a favourable condition, later on there will be an equilibrium where intake equals output, but this is not the case yet at the age of 3 to 4 weeks post partum.

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