Physiopathology of Iodine Nutrition During Pregnancy, Lactation, and Early Postnatal Life

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Iodine is an essential trace element, the only confirmed role of which is the synthesis of thyroid hormones (1). Thyroid hormones in turn play a critical role in the development of the brain (2), a process that occurs in humans during fetal and early postnatal life (3). Consequently, an inadequate supply of iodine occurring during pregnancy and early infancy could critically affect both thyroid function and brain development in young infants.

The objectives of this review are threefold:

1. To discuss published data on the theoretical requirements of iodine in humans, especially during pregnancy, lactation, and early infancy
2. To evaluate the actual intake of iodine of young infants from breast and formula milk
3. To discuss the effects of an extraphysiological supply of iodine on thyroid function during fetal and early postnatal life

RECOMMENDED DIETARY ALLOWANCES OF IODINE

The physiological requirement of iodine is difficult to ascertain and has given rise to much controversy (4). It must be at least equal to the daily amount of hormonal iodine degraded in the peripheral tissues and unrecovered by thyroid, i.e., between 50 and 100 µg/day in adults (5).

The Food and Nutrition Board of the National Academy of Sciences, National Research Council of the United States (6–8), and the European Society for Paediatric Gastroenterology and Nutrition (9) have recommended daily dietary amounts of 30 µg iodine for children aged 0 to 6 months, 45 µg for those 6 to 12 months, 60 to 100 µg for those 1 to 10 years, and 100 to 150 µg for those above 11 years of age. The recommended iodine...
supply during pregnancy and lactation is 125 and 150 μg/day, respectively. Epidemiological and metabolic studies conducted in areas with iodine deficiency and endemic goiter confirmed that the recommended dietary allowance (RDA) of iodine for adults should be at least 100 μg/day (4).

There is an inverse relationship between the daily urinary excretion of iodine used as an index of the dietary intake and the prevalence of goiter in the general population. This prevalence is elevated when the iodine supply is grossly deficient, that is, below 40 μg/day. In contrast, the prevalence is less than 10%, a figure regarded as normal by the World Health Organization (10), when the iodine intake reaches the critical level of 100 μg. A further increase of the intake from 100 to 500 μg/day makes no further reduction in the prevalence of goiter.

More physiopathological findings support the view that an iodine supply of 100 μg/day is adequate for adults. Figure 1 shows that there is a direct relationship between iodine intake and the hormonal iodine content of the thyroid, which is the determining factor in the yield of synthesis of thyroid hormones by the gland (13). This content is markedly reduced when the iodine supply is low, but reaches a normal value of 10 to 20 mg when iodine intake reaches the same critical threshold of 100 μg/day. On the basis of these considerations, the objective of programs of iodine supplementation in the many areas in the world affected by iodine deficiency and endemic goiter is to provide a supply of iodine of at least 100 μg/day in adults (14).

An increase of the RDA of iodine by 25% to 50% during pregnancy and lactation, respectively, appears to be appropriate in order to compensate for the increased loss of iodide through the kidneys, the placenta, and the mammary glands occurring during these periods of life. This aspect has been reviewed by Burrow (15). The figure classically reported for the RDA of iodine for infants aged 0 to 6 months is 35 μg/day (7). This corresponds

![FIG. 1. Relationship between the daily urinary excretion of iodine (I) used as an index of the iodine intake and the exchangeable organic iodine pool of thyroid. [Compiled from Degrossi et al. (11) and Delange and Ermans (12).]]
approximately to 8 μg/kg/day, 5 μg/dl milk, and 7 μg/100 kcal. These are the figures found in most of the starting formula milks. The justification for these figures is not easy to find in the literature, where they constitute a kind of dogma repeated from one paper to the next.

As stated by many authors (16–19), nutrition of the breast-fed infant growing at a satisfactory rate has been the standard against which nutritional requirements have been set. More specifically, the RDA of 40 to 50 μg/day for iodine in infants was based on the amounts of iodine found in breast milk. Whether or not 40 μg/day is actually an ideal intake for infants has never been clearly established (18).

Table 1 summarizes data from the literature on the iodine content of human breast milk. The reports up to the late 1960s are few and are based on a limited series of samples (6,20–22,26). Individual values reported vary from 0.9 to 10 μg/dl and means from 2.8 to 7 μg/dl. These reports probably constitute the substrate for the recommendation of 5 μg iodine/dl milk; however, more recent and comprehensive reports (18,23–25,27) give clearly higher results. Mean values for iodine in breast milk were 7.0, 8.1, and 9.3 μg/dl, respectively, in three large series from Europe and as much as 17.8 μg/dl in one study conducted in the United States (18).

This particularly elevated last figure results from a high and progressively increasing dietary intake of iodine in the United States (28) as a consequence of the use of large quantities of iodine, especially in the bread and dairy industries (16). For example, the iodine intake of young American infants increased from about 400 to 600 μg/day between 1975 and 1978, that is, from 8 to 13 times the recommended RDA (28).

How can the minimal requirement of iodine for infants be objectively estimated? Iodine is required by the growing infant for the build-up of iodine stores in its own thyroid gland, which increase from 0.1 mg at birth (29) to 10 to 20 mg in adolescence and adulthood (12). Consequently, the requirement of iodine in young infants can be derived from metabolic studies by determining the value that results in a state of positive iodine balance. Such
iodine balance studies were conducted in healthy preterm and full-term infants aged approximately 1 month (F. Delange, P. Bourdoux, and J. Senterre, unpublished observations, 1983). Iodine was determined in complete collections of urine and feces taken for at least 3 consecutive days and in a duplicate of the whole quantity of milk ingested.

Results of this study are shown in Table 2. On the basis of unit weight, the iodine intake was similar in both groups, the iodine loss in the feces being low and not significantly different. In contrast, the urinary excretion of iodine was 1.5 times higher in the preterm than in the full-term infants, and the difference was significant. Consequently, the mean retention of iodine in the body was much lower in preterm than in full-term infants, and 40% of the preterm infants were in negative iodine balance, even when the iodine intake was as high as 20 to 30 μg/kg/day. In contrast, all except one of the full-term infants were in positive iodine balance (Fig. 2).

This study indicated that preterm infants require a higher intake of iodine per unit weight than full-term infants in order to achieve a positive iodine balance, i.e., at least 30 to 40 μg/kg/day. This metabolic pattern is due to a high urinary loss of iodine in preterm infants, possibly resulting from renal immaturity. The investigation suggested that the iodine requirement of 8 μg/kg/day or 5 μg/dl/milk in young infants is probably underestimated, especially in preterm infants.

IODINE CONTENT OF BREAST MILK AND FORMULA

Results obtained on breast milk by our group are shown in Table 3. In Brussels we found a mean iodine content of 9.4 μg/dl in breast milk at the fifth postnatal day in a population of lactating women with a dietary intake estimated at 110 μg/day (30) and with a mean urinary iodine of 7.4 μg/dl. The corresponding figures were only 1.3 μg/dl in breast milk in an area of Zaire affected by severe endemic goiter and cretinism, where the iodine
FIG. 2. Comparison of the relationship between iodine intake and iodine retention rate in healthy preterm and full-term infants birthweight (BW). (F. Delange, P. Bourdoux, and J. Senterre, unpublished observations, 1983.)

### TABLE 3. Influence of the dietary and extradietary supplies of iodine on the iodine content of human breast milk; mean ± SEM (n)

<table>
<thead>
<tr>
<th>Area</th>
<th>Remarks</th>
<th>Iodine content (μg/dl)</th>
<th>Dietary intake of iodine (μg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Maternal milk</td>
<td>Maternal urine</td>
</tr>
<tr>
<td>Brussels, Belgium</td>
<td>No iodine overload</td>
<td>9.5 ± 0.6</td>
<td>7.4 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Iodine overload (povidone-iodine)</td>
<td>16.0 ± 1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epidural anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cesarean section</td>
<td>126.7 ± 42.1</td>
<td></td>
</tr>
<tr>
<td>Ubangi, Zaire</td>
<td>Severe endemic goiter + cretinism</td>
<td>1.3 ± 0.1</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>No therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>After iodized oil i.m.</td>
<td>14.6 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>Jena, G.D.R.</td>
<td>Endemic goiter</td>
<td>1.2 ± 0.1</td>
<td>1.9 ± 0.1</td>
</tr>
</tbody>
</table>


intake was only 15 $\mu g$/day and the urinary iodine was as low as 1.8 $\mu g/dl$ (31). Almost similarly low values were observed in Jena, an area in the German Democratic Republic where goiter is endemic.

In Brussels we also found that one single cutaneous application of providone-iodine in the mother at the time of delivery highly significantly increased the iodine content of breast milk, especially when this skin disinfectant was used in preparation for cesarean section. In this case, it resulted in a 13-fold increase in the iodine content of the milk (32).

In Zaire, we observed that one single intramuscular injection of iodized oil administered to women 1 to 30 months before the collection of breast milk increased the iodine content of the milk to a mean value of 14 $\mu g/dl$, which is slightly above the normal. These results indicate that the very simple and cheap procedure of iodine prophylaxis consisting of one single intramuscular injection of iodized oil not only corrects the state of iodine deficiency in the mother but also in the breast-fed infant for at least 30 months. The results reported in Table 3 indicate that the iodine content of maternal milk is critically influenced both by the dietary and extradietary supplies of iodine of lactating mothers.

Table 4 summarizes the results we have obtained for the iodine content of formula milks. Randomly selected casual samples of nine different formula milks currently used in Brussels were collected each month between April 1982 and September 1983. The mean iodine content measured was very similar or even slightly higher than the theoretical content; however, the iodine content measured was systematically lower than the figure of 9.5 $\mu g/dl$ observed in maternal milk in the same area, especially in medical formulas for preterm and sick full-term infants. One exception was soya milk, where the iodine content was higher because of the well-documented goitrogenic properties of soya milk (33).

### Table 4. Iodine content of formula milk in Brussels; mean ± SEM (n)

<table>
<thead>
<tr>
<th>Type of formula</th>
<th>Theoretical</th>
<th>Measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>7.2 ± 0.5 (14)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>7.8 ± 0.5 (14)</td>
</tr>
<tr>
<td>3</td>
<td>4.8</td>
<td>6.7 ± 0.8 (14)</td>
</tr>
<tr>
<td>4</td>
<td>7.0</td>
<td>7.1 ± 0.3 (14)</td>
</tr>
<tr>
<td>Follow-up formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>6.4 ± 11 (14)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>4.2 ± 0.7 (9)</td>
</tr>
<tr>
<td>&quot;Medical&quot; formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm infants 7</td>
<td>3.5</td>
<td>6.6 ± 1.1 (14)</td>
</tr>
<tr>
<td>Semielementary diet 8</td>
<td>3.6</td>
<td>5.0 ± 0.6 (14)</td>
</tr>
<tr>
<td>Soya 9</td>
<td>13.0</td>
<td>14.8 ± 0.7 (11)</td>
</tr>
</tbody>
</table>
Iodine Deficiency

Figure 3 illustrates the most dramatic consequences of iodine deficiency on the thyroid function of neonates as observed in the Ubangi area of Zaire (31). There was marked variability among individuals in Ubangi. As many as 10% of newborns had both a cord serum thyroid-stimulating hormone (TSH) above 100 μg/ml and a cord serum T4 below 3 μg/dl, indicating severe congenital hypothyroidism. In contrast, such a picture was observed in only 0.025% of a newborn population in Brussels (34).

Iodine deficiency in neonates is not a problem limited only to developing countries: In a recent collaborative study (34), the urinary concentrations...
of iodine, used as an index of the dietary supply of iodine, were determined in unselected healthy full-term infants aged 5 days in different places in Europe. The results evidenced marked differences for this variable from one area to another: Relatively elevated values were observed in northern Europe, whereas extremely low values were observed in central and southern Germany. It was shown that a reduction of the iodine supply of newborn populations resulted in an increased frequency of transient alterations of thyroid function and regulation, such as transient hyperthyrotropinemia and transient hypothyroidism.

Since thyroid function is not modified in adults in the same areas, it was concluded from this study that newborn infants are particularly sensitive to the effects of iodine deficiency.

**Iodine Excess**

It was also shown that newborn infants are particularly sensitive to the effects of iodine excess: Elevated urinary concentrations of iodine indicating iodine overload were found in breast-fed infants born to lactating mothers treated by cutaneous application of povidone-iodine at the time of delivery (32). This resulted from the consumption of iodine-contaminated milk. Compared to breast-fed infants with no iodine overload used as controls, the iodine-contaminated infants had unmodified serum concentrations of thyroid hormones but elevated basal (TSH) and TSH responses to thyrotropin-releasing hormone (TRH). These results indicate a slight impairment of thyroid function in the neonates with iodine overload (compensated hypothyroidism). Thyroid function and regulation in the mothers were unmodified. This investigation extends to breast-fed infants born to mothers treated by povidone-iodine, the risk of thyroid impairment following the utilization of iodinated skin disinfectants during the neonatal period (35).

**CONCLUSIONS**

The RDAs of iodine for young infants should be reconsidered and probably increased, especially for preterm infants. Large areas exist in the world today, even in Europe, where the iodine supply of young infants is slightly or clearly insufficient, critically affecting thyroid function and, possibly, brain development. Appropriate measures could and should be considered in the affected areas.

Newborn infants are particularly sensitive to the antithyroid effects of both iodine deficiency and iodine excess. Consequently, neonatal screening for congenital hypothyroidism constitutes a very sensitive index of the presence and action of goitrogenic factors in the environment.
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REFERENCES


