Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy

Mohamed L Chaouki and Moulay Benmiloud

Service d'Endocrinologie, Centre Hospitalo-Universitaire de Batna, Batna, Algeria; Service d'Endocrinologie1, C.P.M.C., Alger, Algeria

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The prevalence of iodine deficiency disorders and the thyroid status of the population were studied in an endemic goitre area in Algeria. After oral administration of lipiodol (0.5 ml), three treated groups of mother–newborn couples were compared to an untreated group: group A, mothers treated 1–3 months before conception; group B, mothers treated during the first month of pregnancy; group C, mothers treated during the third month of pregnancy. Untreated mothers were used as a control (group D). After lipiodol treatment, all newborn babies and mothers were clinically euthyroid. All tested newborn babies were full term and no goitre was observed in the four groups. In the mothers, goitre prevalence and thyrotrophin levels decreased significantly, whereas maternal milk and urinary iodine and serum-free thyroxine levels were significantly higher after treatment. The rate of prematurity, stillbirths and abortions in the treated groups was reduced when compared to the untreated group, whereas placental and birth weights were significantly higher. In group D two cases of neonatal hypothyroidism were detected. Their re-evaluation confirmed that hypothyroidism was transient. Groups A, B and C were statistically different from group D with regard to neonatal thyrotrophin and thyroxine. Positive correlations were found between neonatal thyroxine and birth weights and placental weights on the one hand, and maternal urinary iodine and free thyroxine on the other. Consequently, these data indicate that oral administration of lipiodol before or during the first trimester of pregnancy normalizes thyroid function in newborn babies and mothers, increases placental and birth weight and reduces the frequency of iodine deficiency disorders. Lipiodol at this dose and during the first trimester of pregnancy had no deleterious effects and may prevent hypothyroid or neurological cretinism.

Mohamed Lamine Chaouki, Service d’Endocrinologie, Centre Hospitalo-Universitaire de Batna, Route de Tazoul 05000, Batna, Algeria

In severely iodine-deficient areas, abnormalities of thyroid function can be found in pregnant women and their newborn babies (1–4). The main dysfunction is hypothyroxinaemia. During a pilot screening programme for neonatal hypothyroidism (NH) we have demonstrated an increased incidence of NH in northeastern Algeria (5). Although several cases were transient, hypothyroidism occurred during a critical stage of brain maturation after birth. Positive correlations between maternal and fetal thyroid status also have been described in iodine-deficient environments (3–6). Various reports have put forward the hypothesis that the neurological signs present in endemic cretinism could be secondary to maternal and fetal hypothyroxinaemia during pregnancy (6, 7) and a low iodine content in breast-feeding could be responsible for hypothyroxinaemia in the newborn baby. These as well as other iodine deficiency disorders are modulated by the severity of the iodine deficiency.

There is also a general agreement that iodine prophylaxis can prevent these disorders (1, 4, 8) but a doubt persists as to the best time and form of implementation. This is a rather important point, considering that in developing countries access of women to medical care can be difficult.

In this report we present a study of the effects of oral administration of iodized oil on maternal and newborn thyroid function and its secondary effects on pregnancy. We have attempted also to determine the optimal period of oral administration and the duration of protection by a small dose of lipiodol.

Patients and methods

This study was conducted in a mountainous area in northeastern Algeria (mean altitude 1200 m) described previously (5, 7). The epidemiological profile of the area was as follows: goitre prevalence 51.3%, endemic cretinism 1.1%, iodine level of water 42.5 ± 10.2 nmol/l, mean concentrations of serum TSH 7.9 ± 2.7 mU/l, serum T4 117.4 ± 24.5 nmol/l, urinary iodine 127.6 ± 37.8 nmol/l and urinary thiocyanate 161.3 ± 37.8 μmol/l.

During an iodized oil prevention programme, four
groups of mother–newborn couples were selected at delivery time. The date of conception was determined by the date of the last menses, corrected by subtraction of 9 months from the date of delivery when the baby weight was normal. Three had received, per os, 0.5 ml of iodized oil (lipiodol, 240 mg of iodine). In group A (N = 213) the mothers were treated 1–3 months before conception. In group B (N = 190) and group C (N = 151) iodized oil was administered, respectively, during the 1st and 3rd months of pregnancy. In group D (N = 982) the mothers received no treatment.

All mothers at treatment time and after delivery were submitted to a full clinical examination to exclude thyroid dysfunction; thyroid volume was assessed according to Delange et al. (9). Placental weight also was recorded at delivery time for each woman.

All newborn babies were examined for signs of thyroid dysfunction or goitre and their birth weight was recorded. The urinary iodine concentration of each mother was assayed according to Garry et al. (10) on a casual sample. Blood samples from all the mothers were collected for assay of TSH (University Hospital, Batna, Algeria), free T4 (RIA Gnost Behring Werke AG, Marburg, Germany) and antithyroglobulin and antithyroid antibodies (Thymune T and Thymune M, Wellcome Diagnostics, UK). The T4 and TSH (CIS Bio International, Gif-sur-Yvette, France) were assayed from cord blood for all newborn babies. Recall criteria were TSH > 40 mU/l and T4 < 51 nmol/l. The acoustic reactions of all the infants were tested with a baby reactomer (Audiotest AT3, Viennatone) delivering 40 dB of control sound alternatively on the right and left side 1 month after birth.

Bone maturation was determined on standard X-rays of the hand, wrist and knee according to Pyle (11) and Greulich and Pyle (12). Results were expressed as means ± 1 SEM.

Statistical assessment was made using variance and linear regression analyses. The significance of these results was confirmed by analysis of the confidence intervals using Wilcoxon’s non-parametric test.

Results

The mean age of the pregnant women was 29 ± 8 years (range 19–39). The mothers in all groups were clinically euthyroid and the visible goitre prevalence was similar in the four groups (Table 1). After iodized oil the prevalence of visible goitres was significantly and similarly lower (p < 0.01) in the three treated groups. Furthermore, there was a marked decrease of the goitre volume in 50% of the treated group, whereas there was no significant change in the untreated group. There were no side-effects during the follow-up after iodine treatment.

The mean maternal urinary iodine concentrations were lower than 157.6 nmol/l in the four groups at the beginning of the study. At delivery time the urinary iodine concentrations were significantly higher (p < 0.001) in the treated groups (Table 2). Although all individual values were higher than 709 nmol/l, in group A they were significantly lower (p < 0.05) than those of groups B and C at birth. Six

<table>
<thead>
<tr>
<th>Group</th>
<th>Before lipiodol</th>
<th>At delivery</th>
<th>6 months after delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine</td>
<td>Milk</td>
<td>Urine</td>
</tr>
<tr>
<td>A (N = 213)</td>
<td>149 ± 0.4</td>
<td>748 ± 2.1b</td>
<td>520 ± 11.8</td>
</tr>
<tr>
<td></td>
<td>(118–165)</td>
<td>(709–788)</td>
<td>(338–709)</td>
</tr>
<tr>
<td>B (N = 190)</td>
<td>157 ± 1.6</td>
<td>803 ± 3.9b</td>
<td>559 ± 10.8</td>
</tr>
<tr>
<td>C (N = 151)</td>
<td>133 ± 3.1</td>
<td>780 ± 3.1b</td>
<td>551 ± 13.4</td>
</tr>
<tr>
<td>D (N = 982)</td>
<td>141 ± 0.7</td>
<td>141 ± 0.4b</td>
<td>307 ± 3.2</td>
</tr>
</tbody>
</table>

Table 1. Prevalence (%) of visible goitres.

- p < 0.01 for all variables when comparing values before and after lipiodol.
- Not significant.

Table 2. Maternal iodine (nmol/l) in urine and milk before and after lipiodol.

- Results are expressed as means ± 1 SEM and ranges are given in parentheses.
- b p < 0.001: differences between the levels before lipiodol and at delivery.
- c p < 0.01: differences between the levels at delivery for urine and 1 month after for milk, compared to 6 months later.
- d Not significant.
months after delivery the mean urinary iodine levels in groups A, B and C were lower than at delivery (p < 0.01), all individual values being lower than 433 nmol/l.

The maternal milk iodine level measured 1 month after delivery was significantly higher in groups A, B and C compared to group D (p < 0.001). It was lower also in group A compared to groups B and C (p < 0.05).

Six months after delivery the iodine level decreased significantly compared to that at 1 month but remained higher than in group D.

The biochemical status of the mothers is summarized in Table 3; none was hyperthyroid. The mean serum free T4 was within the normal range for each of the four groups, but increased significantly after treatment in groups A, B and C (p < 0.01) compared to group D and to the pretreatment levels. There was no significant difference between groups A, B and C. Before treatment the mean serum TSH was normal in the four groups and decreased significantly in groups A, B and C compared to group D (p < 0.01). There was no statistically significant increase at 6 months. In the treated groups the abortion rate (0%), prematurity rate (10.8%) and still-birth rate (9.0%) were significantly lower (p < 0.001) than in the untreated group (19.0%, 14.3% and 20.4%, respectively). The mean placental weights in groups A, B and C together (583 ± 76 g) or taken separately were significantly higher (p < 0.001) compared to D (562 ± 51 g). There was no significant difference between A, B and C. These results were confirmed by analysis of the confidence intervals of the data using the Wilcoxon method.

There was neither iodine goitre nor clinical or biochemical hypothyroidism in the treated groups. While two cases of neonatal hypothyroidism were detected in group D.

In Table 4 the data obtained in the newborn babies are summarized. The mean birth weights in groups A, B and C were statistically higher than in group D (p < 0.01). Acoustic reaction was normal in all subjects, excluding any gross hearing defects. The mean serum TSH and the mean serum T4 levels were, respectively, lower and higher in groups A, B and C as compared to D (p < 0.001). Moreover, in group D 3% (29/982) of the babies had a cord TSH level greater than 20 mU/l but a T4 level of 50.31–55.47 nmol/l. The cord TSH levels of two hypothyroid babies were 159 and 200 mU/l and the T4 levels were 23.22 and 19.35 nmol/l. This was confirmed by measurement of serum TSH (92 and 124 mU/l) and serum free T4 (4.38 and 2.83 pmol/l) levels.

The hormone treatment (50 μg of l-thyroxine) in both of these infants was started respectively, on day 10 and on day 15 after birth. Treatment was interrupted for 2 weeks at age 18 months for re-evaluation. The thyroid scan after thyroid stimulation by TSH (50 U) demonstrated a thyroid gland in the normal position. Serum TSH and free T4 levels remained normal in successive measurements after interruption of l-T4 administration. The bone age was normal during follow-up and it was concluded that the hypothyroidism was transient in both infants. The two newborn babies could not be differentiated from the others on birth weight, gestational age or clinical examination at birth but both mothers had abnormal biological profiles as compared to treated and untreated mothers (urinary

\[ *\text{Results are expressed as means ± 1 SEM. Normal ranges: TSH, 0.1-4 mU/l.} \]

\[ \text{b} p < 0.01: \text{differences between the levels before lipiodol and at delivery.} \]

\[ \text{c} p < 0.05: \text{differences between the levels at delivery and 6 months later.} \]

\[ \text{d} \text{Not significant.} \]
iodine 118.2 and 110.32 nmol/l; TSH 5.9 and 6.3 mU/l; free T₄ 9.67 and 9.03 pmol/l.

There were negative correlations between free T₄ and TSH levels of the mothers (p < 0.01, r = −0.72) and between the maternal free T₄ and the newborn TSH (r = −0.75) in all groups. Positive correlations (p < 0.01, r = 0.75) were found between neonatal T₄ and birth weight on the one hand and placental weight on the other (p < 0.01, r = 0.69) in all groups. Also, there were positive correlations (p < 0.001) between neonatal T₄ on the one hand and maternal urinary iodine concentration (r = 0.82) and free T₄ (r = 0.78) on the other in all groups. Finally, the correlation was highly positive (p < 0.001) between milk iodine 1 month and 6 months after delivery and urinary iodine excretion at delivery (r = 0.79) and 6 months after delivery (r = 0.80).

Discussion

Although high, the prevalence of iodine deficiency disorder (IDD) found in this region of Algeria was lower than that reported previously from other countries (13). None the less, this study confirmed the causal role of iodine deficiency because its prevention by administration of iodized oil markedly reduced the prevalence of thyroid dysfunction. The therapeutic trial also has confirmed the efficiency of small doses of oral lipiodol (0.5 ml). The 50% decrease in visible goitres is in good agreement with results obtained for larger doses by injection (14, 15). Tonglet et al. have used smaller doses (0.10 and 0.25 ml) in Zaïre, which also were effective in decreasing the thyroid volume in young adults (16).

The maternal thyroid function was improved as indicated by changes in several biological parameters: decreased serum TSH and increased serum free T₄ and urinary iodine excretion in all the treated groups as compared to pretreatment levels. Also, as in other endemias (2, 17), we observed a decrease in both prematurity and stillbirth rates and no abortion was reported amongst the treated subjects. The placental weight was increased in the treated mothers. The significance of this effect of iodized oil on the placenta with regard to the improved hormonal status of the fetus needs further clarification. Also, iodine administration to the mother increased the birth weight of the babies in this iodine-deficient area, confirming the report of Thilly et al. (17).

The main impact of prevention was to normalize fetal hypothyroxinaemia, as shown by the cord T₄ level at birth. This prevents the deleterious effects of hypothyroxinaemia, particularly on the central nervous systems (18–21). The neurological signs observed in the child (deaf-mutism, spastic rigidity, hyper-reflexia and gait disorders) result from lesions acquired at the end of the first or the beginning of the second trimester (22). Maternal thyroid status appears to be a determinant of IDD genesis in the infant, in view of the strong correlation between maternal and the neonate thyroid function on the one hand (4, 5) and the protective role of maternal thyroxine on fetal development, demonstrated at least in the animal (23), on the other hand. Although in the physiological state fetal thyroid function is autonomous (24), it is not totally independent of that of the mother. In any case fetal, neonatal and maternal thyroxinaemia are modulated by the severity, the date of occurrence and the duration of the maternal iodine deficiency. The deficiency in iodine can be aggravated further by a goitrogen-rich diet (20, 25).

In areas of severe iodine deficiency a high incidence of neonatal hypothyroxinaemia has been reported (5, 26). Although mostly transient, the low level of circulating thyroxine at a critical stage of brain development could in part explain the mental retardation reported previously (27). At different stages during early or late fetal life or after birth, variations in the level of hypothyroxinaemia could explain the varied spectrum of physical and mental abnormalities. Amongst these disorders the most severe is endemic cretinism (4, 6) but, like the others, it can be prevented by iodine prophylaxis. To be efficient, treatment should anticipate pregnancy or, at the very latest, precede the second trimester (1, 28): when delayed, it may be only partially effective and spastic diplegia may not be prevented (8). Recent findings of GR DeLong (pers. comm.) in China confirm that iodine administration during the first and second trimester, but not after, prevents neurological cretinism.

Because of the potential deleterious effects of high doses of iodine, we have used a lower dose than those used in the past (1, 4, 8, 29). This gave a 1-year protection and thus a coverage that was shorter than intramuscular administration. Six months after birth, 82% of the urinary iodine levels were lower than 433 nmol/l (55 µg/l) and this was confirmed further by the fact that 90% of the milk iodine levels were lower than 395 nmol/l (50 µg/l). This could mean an insufficient iodine supply to the nursing (30), because in developing countries such as Algeria they may depend entirely on breast-feeding for 18–24 months. However, it is likely that the first trimester, which is critical for brain maturation, is adequately covered because the mean milk iodine levels at 1 month were twice as high in the treated groups compared to the control, and close to the levels found in iodine-sufficient areas. None the less, it would be advisable to administer a second dose of iodized oil during the first semester after delivery, 1 year after the first one.

In conclusion, this study demonstrates that oral administration of small doses of iodized oil before or early in pregnancy is an effective, simple and cheap means of preventing deleterious effects of iodine deficiency in newborn babies when iodized salt is not available for long-term prevention. Repetition of these doses would avoid the side-effects from large doses as well as the danger from injections.
References


