Reviews/Analyses

Administration of iodized oil during pregnancy: a summary of the published evidence*

F. Delange

This brief review of the available studies confirms that the administration of iodized oil before or during pregnancy prevents endemic cretinism and brain damage by correcting iodine deficiency and thyroid function in pregnant women, fetuses, neonates, infants and children. The potential benefits derived from using iodized oil immediately before or during pregnancy greatly outweigh the potential risks in areas of moderate and severe prevalence of iodine-deficiency disorders, where iodized salt is not yet available.

The administration of iodized oil to entire populations, and especially to women of childbearing age and during pregnancy, has been proposed as an emergency prophylactic and therapeutic approach in areas with severe iodine deficiency complicated by endemic cretinism where universal salt iodization has not yet been successfully introduced (1). This procedure prevents brain damage due to iodine deficiency in the fetus and the neonate.

Findings

Iodized oil programmes have conclusively been shown to be effective in preventing and treating endemic goitre, and also in preventing endemic cretinism (2-13) and the alterations of neuropsych-intellectual development which are frequently encountered in non-cretinous individuals (13-38). However, adverse side-effects have been reported in non-pregnant adults due to the administration of iodine far in excess of physiological need. For example, in a pilot study of 14 subjects in the Solu region of the Nepalese Himalayas, Croxson and colleagues (39, 40) reported a significant fall in serum T3 (triiodothyronine) and a rise in serum TSH (thyroid-stimulating hormone) concentrations over a period of 4-10 days (mean, 6 days) in 8 subjects with small goitres soon after receiving intramuscular (IM) injections of 400mg of iodine in oil, which suggests an acute inhibitory Wolff-Chaikoff effect. In addition, three other subjects with large multinodular goitres developed biochemical hyperthyroidism. These findings in pilot studies are compatible with well-documented iodine-induced thyrotoxicosis which occurred in severely iodine-deficient populations following the introduction of iodine prophylaxis by iodized salt (41-46). There are a few reports of iodized oil-induced hyper- or hypothyroidism in public health programmes, sporadic cases of hyperthyroidism having been reported from Ecuador (47), Peru (48) and Argentina (49), but these were not detected in large-scale programmes in New Guinea (2, 50), Zaire (6, 9, 12, 51), Nepal (38, 40, 52), Algeria (53), Indonesia (54, 55) and China (56, 57). Since many of these interventions were conducted under particularly difficult environmental conditions, adverse reactions to therapy could easily have escaped detection (58).

In contrast, detailed studies have been carried out on the effects of iodized oil administered to women just before or during pregnancy with special attention to the short- and long-term side-effects of iodized oil on thyroid function in the mother, neonate, infant and child (59). In carefully executed studies in New Guinea on the effects of iodized oil administered before or during pregnancy to prevent endemic cretinism (4, 11), biological tests examining thyroid function were rarely available (20, 22) because of particularly difficult environmental condi-

---

* This article is based on material presented at a WHO Consultation on the Safety of Iodized Oil for Pregnant Women, Geneva, 13-14 September 1994. See also: Safe use of iodized oil to prevent iodine deficiency in pregnant women on pages 1-3 of this issue. Requests for reprints should be sent to Nutrition Unit, World Health Organization, 1211 Geneva 27, Switzerland.

' Department of Paediatrics, Hospital Saint-Pierre, Brussels, Belgium.

Reprint No. 5679
Table 1: Effects of iodized oil, given just before or during gestation, on the thyroid function of mothers, neonates, infants and children.* The results are given as means ± SE except where otherwise indicated.

<table>
<thead>
<tr>
<th>Region and epidemiology</th>
<th>Protocol</th>
<th>Mothers at delivery</th>
<th>Neonates</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North-eastern Algeria</strong></td>
<td>Placebo-controlled randomized study (n = 1536)</td>
<td>Urinary iodine: 1.8 µg/dl</td>
<td>TSH: 4.1 mIU/l</td>
<td>T&lt;sub&gt;s&lt;/sub&gt;: 6.7 µg/dl</td>
</tr>
<tr>
<td>Urinary iodine: 1.6 ± 0.5 µg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of goitre:</td>
<td>Placebo (n = 982) vs iodized oil (n = 554)</td>
<td>Urinary iodine: 9.4 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TSH: 2.1 mIU/l&lt;sup&gt;b&lt;/sup&gt;</td>
<td>T&lt;sub&gt;s&lt;/sub&gt;: 10.4 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>— global population: 53%</td>
<td></td>
<td>Urinary iodine: 10.1 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
<td>TSH: 2.1 mIU/l&lt;sup&gt;b&lt;/sup&gt;</td>
<td>T&lt;sub&gt;s&lt;/sub&gt;: 11.0 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>— pregnant women (visible goitre rate): 47%</td>
<td>Iodized oil 0.5 ml (240 mg/l) orally:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of cretinism: 1%</td>
<td>a) 1–3 months before conception (n = 213)</td>
<td>Urinary iodine: 9.8 µg/dl&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>TSH: 1.9 mIU/l&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>T&lt;sub&gt;s&lt;/sub&gt;: 10.8 µg/dl&lt;sup&gt;bc&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>b) During the first month of gestation (n = 190)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c) During the third month of gestation (n = 151)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Ubangi area, northern Zaire** | Placebo-controlled, longitudinal, randomized study (n = 983) | Urinary iodine (µg/dl): | Untreated (n = 246) | Untreated (n = 195) |
| Urinary iodine: 15.5 ± 1.3 µg/day (n = 243) | 3.63 (3.30–3.99)<sup>c</sup> | <5: 65% | | |
| Prevalence of goitre: | <2: 25% | | | |
| — global population: 51% | | | | |
| — pregnant women: 75% | | | | |
| Prevalence of cretinism: | Placebo (n = 484) vs iodized oil (n = 499), 1 ml IM (480 mg/l) during the last two trimesters of gestation (mean: 28th week) | Serum TSH (mIU/l): | 6.08 (5.64–6.56)<sup>c</sup> | 18.45 (16.52–20.60)<sup>c</sup> |
| | | T<sub>s</sub>: 9.1 ± 0.3 µg/dl | T<sub>s</sub>: 8.2 ± 0.3 µg/dl | |
| | | T<sub>s</sub>: 187 ± 5 ng/dl | T<sub>s</sub>: 86 ± 5 ng/dl | |

**Mothers:**
The abortion, prematurity and stillbirth rates were lower in the treated than in the untreated group (P < 0.001)
None became hyperthyroid
At 6 months, urinary iodine remained twice higher and TSH twice lower in the treated lower in the treated group than in the controls respectively

**Infants:**
The incidence of hypothyroidism was 2/982 in the untreated group and 0/554 in the treated group
Hypothyroidism was only transient

**Infants + children:**

* Untreated

| | | | | | |
| Urinary iodine (µg/dl): | 0–84 months: stable 1.5–3.6 | | | | |
| Serum TSH (>10 mIU/l): | 0–36 months: 46–49% | 36–84 months: 59% | | | |
| Serum T<sub>s</sub> (µg/dl): | 0–84 months: low, stable | | | | |
| Overt clinical and severe biochemical hypothyroidism (endemic myxoedematous cretinism): | 8.3% | | | | |
(Table 1: continued)

<table>
<thead>
<tr>
<th>Treated (n = 256)</th>
<th>Treated (n = 199)</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary iodine (µg/dl)</td>
<td>Serum TSH (mU/l):</td>
<td>Serum TSH (mU/l):</td>
</tr>
<tr>
<td>56.6 (51.3–62.5)</td>
<td>2.67 (2.49–2.86)</td>
<td>7.19 (6.67–7.76)</td>
</tr>
<tr>
<td>&lt;5: 8%</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;: 14.2 ± 0.3 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;: 11.2 ± 0.3 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>&gt;1000: 5%</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 154 ± 3 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 62 ± 3 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Ntcheu district, Malawi**

<table>
<thead>
<tr>
<th>Urinary iodine: 3.3 ± 0.1 µg/dl</th>
<th>Placebo-controlled randomized study (n = 627)</th>
<th>Placebo (n = 404) vs iodized oil 0.5 ml (240 mg) IM or orally during the last trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of goitre: 59%</td>
<td>Urinary iodine: 3.3 µg/dl</td>
<td>Urinary iodine: 4.7 µU/l</td>
</tr>
<tr>
<td>Prevalence of cretinism: 1%</td>
<td>Serum TSH: 10.5 ± 3.4 µg/dl</td>
<td>Serum TSH: 216 ± 76 ng/dl</td>
</tr>
<tr>
<td></td>
<td>T&lt;sub&gt;4&lt;/sub&gt;: 8.6 ± 2.3 µg/dl</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 65 ± 54 ng/dl</td>
</tr>
<tr>
<td></td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 216 ± 76 ng/dl</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 216 ± 76 ng/dl</td>
</tr>
<tr>
<td>Untreated (n = 404)</td>
<td>Untreated (n = 400)</td>
<td>Untreated (n = 147)</td>
</tr>
<tr>
<td>Treated by iodized oil IM (n = 147)</td>
<td>Serum TSH: 2.8 µU/l</td>
<td>Serum TSH: 5.9 µU/l</td>
</tr>
<tr>
<td>Urinary iodine: 28.5 µg/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;: 28.8 ± 3.1 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;: 10.5 ± 2.7 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum TSH: 2.8 µU/l</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 208 ± 87 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 66 ± 10 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 12.8 ± 3.1 µg/dl&lt;sup&gt;b&lt;/sup&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 208 ± 87 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 208 ± 87 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 231 ± 70 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 231 ± 70 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>T&lt;sub&gt;3&lt;/sub&gt;: 231 ± 70 ng/dl&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Compiled from references 7–9 and 61–68, and from J. Vanderpas & B. Swannen, personal communication.

* Significant difference compared with the untreated group (P < 0.001).

* These results are geometric means (±SEM; +SEM).
tions. Pharoah (4) reported very low levels of serum protein-bound iodine (PBI) in untreated mothers who delivered cretins, whereas normal values were still found in treated mothers who delivered normal infants 3-4 years after receiving iodized oil injections. Pretell and colleagues (60) reported that in an area of severe iodine deficiency in the Peruvian Andes (daily urinary excretion of iodine, 25 μg; prevalence of visible goitre, 52-59%; and prevalence of cretinism, 1.0-3.6%), umbilical cord serum T₄ (thyroxine) and free T₃ levels were much lower, and TSH levels higher, than in controls from an iodine-replete area. The results for the same variables were normal in neonates born to mothers injected with iodized oil before or during early pregnancy. No adverse side-effects were observed either in mothers or neonates.

The most detailed studies of iodized oil given during pregnancy have been conducted in Zaire (7-9, 12, 61-65), Algeria (66, 67) and Malawi (65, 68) in areas of severe iodine deficiency and endemic goitre, complicated by cretinism (Table 1). The doses of iodized oil were 1 ml IM (480 mg) in Zaire, and 0.5 ml IM or orally in Algeria and Malawi. Time of administration varied from just before pregnancy in Algeria to the third trimester of gestation in Zaire. The result was a systematic and dramatic increase in maternal iodine supply, with only occasional iodine overload (5% of treated women in Zaire had urinary iodine levels above 1000 μg/dl at the time of delivery). Nevertheless, thyroid function in mothers, which frequently indicates hypothyroidism in the absence of therapy, was normal in all treated mothers at delivery; their serum TSH, T₄ and T₃ levels were similar to those observed in mothers in iodine-replete areas (69, 70). In addition, not a single woman exhibited biochemical evidence of hyperthyroidism and the prevalence of goitre markedly decreased in those who had been treated.

In the absence of therapy for mothers, thyroid function was severely impaired in a large number of neonates (in the Ubangi area of Zaire, 14% of infants had cord serum TSH above 100 μU/ml and T₄ below 4 μg/dl). The extent of deviation from normal values in infants was more severe than in mothers and was directly related to the severity of the iodine deficiency and hypothyroidism present in mothers. Once again, iodized oil administered to mothers entirely normalized the thyroid function in neonates, and the correction occurred regardless of the stage of pregnancy — from the first month to late in the third trimester — at the time of therapy.

In seven years of follow-up after treatment of mothers with iodized oil, no case of hyperthyroidism was reported in either mothers or children. Depending on the dose and the stage of pregnancy at which it was given, the status of iodine nutrition of infants and children (evaluated by ascertaining urinary iodine concentrations) progressively deteriorated with age, reverting to the degree of iodine deficiency found in untreated individuals from the age of 2 years onwards. Nevertheless, clinical and biochemical hypothyroidism was largely prevented in infants born to treated women, and when they occurred, they were frequently transient in nature. Finally, treating pregnant women with iodized oil resulted in decreased incidence of abortions, prematurity and stillbirths, and an increased birth weight.

These positive results stand out in contrast to the interpretation of the results of a single study, which has frequently been reported in the literature in the last decade (20, 71-74). The study was conducted in parts of Bhutan and India known for severe iodine deficiency (more than 50% of the population with urinary iodine/creatinine ratio below 25 μg/g creatinine and goitre prevalence varying from 60% to 80%). Iodized oil (1 ml IM) was administered to schoolchildren, women of reproductive age, and pregnant women. Cord serum TSH and T₄ were measured in a group of 154 neonates born to mothers who had been injected during the second half of the third trimester of pregnancy (mean of 3.5 weeks before delivery). Selection criteria for neonates and the range of the time interval between injection and delivery were not reported. Sixteen of the 154 infants (10.4%) had cord serum TSH above 50 mU/l and cord T₄ below 3 μg/dl, indicating neonatal biochemical hypothyroidism. The investigators concluded that the iodized oil administered during pregnancy induced thyroid failure in the neonates, and consequently that oil therapy should be rejected as a prophylactic measure during pregnancy.

This interpretation is seriously to be questioned for two reasons. First, in the absence of results for urinary iodine in mothers, there is no evidence that the mothers were indeed injected and were iodine overloaded. Second, and more important, the same incidence of neonatal biochemical hypothyroidism (7.5-13.3%) was reported in the study areas in the absence of an iodized oil programme. Consequently, the study provides no evidence that the iodized oil administered to pregnant women had adverse effects on the neonates.

**Conclusion**

Detailed studies provide conclusive evidence that the administration of iodized oil prior to, or during, pregnancy prevents endemic cretinism and brain damage by correcting iodine deficiency and thyroid function in pregnant women, fetuses, neonates, in-
Résumen
Administration d’huile iodée pendant la grossesse: résumé des études publiées
Des études détaillées montrent de façon concluante que l’administration d’huile iodée avant ou pendant la grossesse contribue à prévenir le crétinisme endémique et les lésions cérébrales en corrigant la carence en iode et la fonction thyroïdiennne chez la femme enceinte, le fœtus, le nouveau-né, le nourrisson et l’enfant. Pour prévenir les lésions neurologiques, il est essentiel de corriger la carence en iode avant la grossesse ou au début de celle-ci. La correction de l’hypothyroïdisme maternel, fœtal et néonatal peut se faire à n’importe quel moment de la grossesse, même au cours du dernier trimestre. La durée de la correction post-natale de la fonction thyroïdienne dépend de la dose d’huile iodée administrée à la mère; elle est par exemple d’environ deux ans après administration de 1 ml par voie orale ou intramusculaire, mais seulement de six mois pour 0,5 ml. En dépit des doses massives d’iode qui ont été administrées, aucune anomalie de la fonction thyroïdienne induite par cet élément n’a été démontrée de façon concluante au moment de l’accouchement ou ultérieurement chez les femmes enceintes et leurs enfants qui ont fait l’objet d’un suivi à court ou à long terme.
Les avantages potentiels de l’administration d’huile iodée immédiatement avant la grossesse ou au cours de celle-ci compensent largement les risques potentiels dans les régions où la prévalence des troubles dus à une carence en iode est modérée à forte et où l’on ne prévoit pas de distribution de sel iodé avant un an ou deux.

References


Administration of iodized oil during pregnancy


67. Chaouki ML, Benmiloud M. Prevention of iodine deficiency disorders by oral administration of lipiodol


69. **Berghout A et al.** Thyroid function and thyroid size in normal pregnant women living in an iodine replete area. *Clinical endocrinology*, 1994, 41: 375–379.


