

# Iodized Oil: Its Role in the Management of Iodine Deficiency Disorders

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**A**lthough universal salt iodization has been used as the most effective method of providing iodine supplementation, in areas where salt iodization program has failed, or when iodized salt is not widely available, iodized oil can be used for iodine supplementation. Following administration of iodized oil, iodine is continuously released from the lipid stores over long periods of time. The effect may last for one year after oral and up to 3-7 years after intramuscular administration, helping to prevent endemic goiter, physical and psychomotor retardation, and the undesirable pre- and postnatal complications of iodine deficiency. Iodized oil administration decreases the size of goiter, reverses hypothyroidism, improves psychomotor performance and corrects auditory disturbances caused by iodine deficiency. Dermatologic complications, iodine induced hyperthyroidism and hypothyroidism may occur following its use, but enhancement of thyroid autoimmunity and thyroiditis have rarely been reported. The use of iodized oil during pregnancy has no deleterious effects on the thyroid function of the offspring.

**Key Words:** Iodized oil, Iodine deficiency disorders, Endemic goiter, Iodine induced hyperthyroidism

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## Introduction

Although millions of people with iodine malnutrition suffering from goiter, growth

and mental retardation have benefited from iodine supplementation, one third of the world population still live in areas of iodine deficiency.<sup>1</sup>

Universal salt iodization (USI) has been used as the simplest and most effective means of providing iodine supplementation. It has resulted in sustainable elimination of iodine deficiency disorders (IDD) in many countries of the world.<sup>2</sup> In some developing countries with iodine deficiency, iodination of salt, bread or water has failed to eliminate IDD; various socioeconomic, climatic, or geographic factors have made systematic and sustainable iodine supplementation difficult and unsuccessful. In such conditions and at the outset of implementation of an IDD prevention program, administration of large quantities of iodine in the form of slowly absorbable iodized oil has been successful in prevention of IDD and in treatment of goiter and hypothyroidism caused by iodine deficiency.<sup>3-8</sup> It is the intention of this paper to review the beneficial and side effects of iodized oil administration in the prevention and control of IDD.

**General characteristics:** Iodized oil is the product of addition of iodine to double bonds of the unsaturated fatty acids of certain plant oils. Administration of iodized oil preparations owes its success to the slow and continuous release of iodide from the lipid stored

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over long periods of time from various pools, particularly adipose tissue.<sup>9</sup>

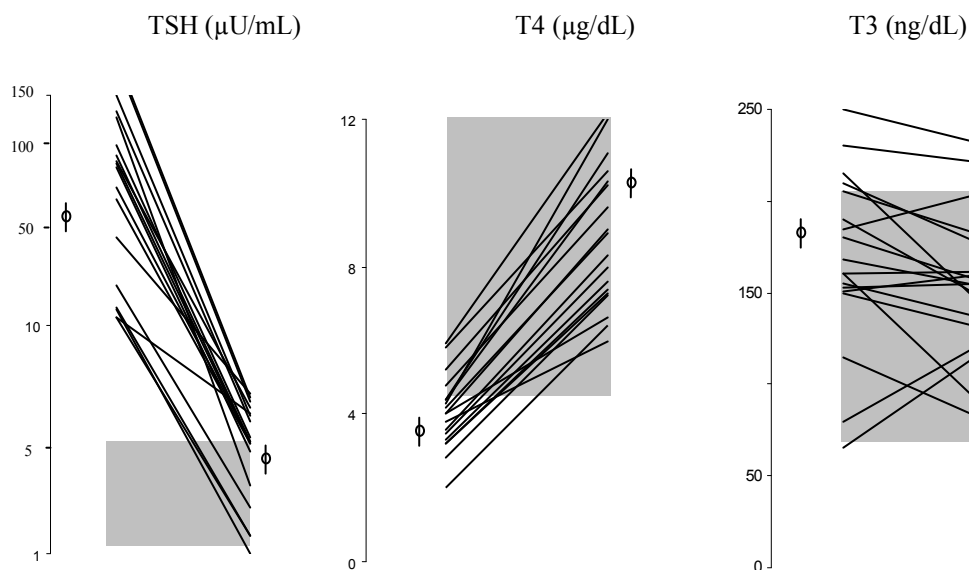
Intramuscularly iodized oil supplementation causes a longer half-life than the oral form. The half-life of iodide, released from stored iodized oil after intramuscularly injection has been reported to be between 5.1 and 5.6 months;<sup>3,4</sup> however, other studies have reported different half-lives. The maximum urinary iodine concentration appears 3 months after intramuscularly injection. The decline in urinary iodine concentration is at least bi-exponential, with an early fast period

of one week required to decrease urinary iodine by 50% ( $t_{1/2}$ ) of approximately one week, and a slower component with a  $t_{1/2}$  months or more.<sup>10</sup> Intramuscular administration of iodized oil appears to help avoid some of the extremely high early iodide concentrations seen after oral intake of iodized oil.

Diarrheal disease<sup>11</sup> goiter,<sup>12</sup> iron deficiency,<sup>13</sup> malnutrition,<sup>14</sup> selenium deficiency,<sup>15</sup> use of manioc or cassava,<sup>16</sup> and worm infestation,<sup>17</sup> may affect the response to iodized oil administration (Table 1).

**Table 1. Factors influencing the efficacy of iodized oil administration**

Factor	Mechanism	Reference No.
Diarrheal disease	↓ Availability of iodine	11
Infestation (ascaris, entameba)	↓ absorption or retention of iodized oil	17
Iron deficiency	↓ Thyropeoxidase activity	13
Long standing goiter	↓ Thyroid reserve	12
Malnutrition	↓ Peripheral availability of iodine	14
	↓ Thyroid function	
Selenium deficiency	↓ 1, 5- Iodothyronine denominated activity	15
Use of manioc or cassava	Formation of thyocyanate and Competitive inhibition of iodide transport	16



**Fig. 1. Individual values and mean ( $\pm 1$  SEM) level (bars) of serum thyrotropin (TSH), thyroxine (T4), and Triiodothyronine (T3) in schoolboys with iodine deficient hypothyroidism (aged 7 to 15 years) before therapy (closed circles) and four months after the administration of iodized oil (open circles). The shaded areas represent the normal ranges in euthyroid children in Tehran.**

**Prevention and treatment of iodine deficiency disorders:** Iodized oil has been highly successful as long-term replacement therapy for IDD. The method is inexpensive, approximately € 0.80 per dose, and can be easily implemented through local health services. The effect may last for 7 years in adults and 3-5 years in children after intramuscular injection and for 1 year after oral administration.<sup>10,18</sup>

The use of iodized oil in the prevention of endemic goiter was initiated by Clarke et al.<sup>19</sup> Shortly thereafter McCullagh<sup>20</sup> and Hannesy<sup>21</sup> reported the reduction of goiter rate in controlled trials of iodinated oil given intramuscularly to goitrous subjects. Iodized oil reduces goiter size,<sup>22,23</sup> improves mental and psychomotor performance in schoolchildren,<sup>24,25</sup> and prevents undesirable pre- and postnatal complications of iodine deficiency.<sup>26</sup> Iodized oil has failed to reverse hypothyroidism in adolescent and adults with endemic myxedematous cretinism,<sup>27</sup> it has however been shown to be effective in restoring normal

thyroid function in children with cretinism up to 4 years of age, being only partially beneficial in older children.<sup>28</sup> In a study of schoolchildren with goitrous hypothyroidism due to iodine deficiency, it was shown that T4 and TSH reverted to normal in girls<sup>8</sup> and boys.<sup>29</sup> Fig. 1 shows changes in serum T4, T3 and TSH before and 4 months after intramuscular injection of 480 mg iodized oil, effects which persisted 1-3 years after iodized oil injection.<sup>30</sup> Table 2 shows normalization of serum TSH and T4 concentrations for up to 36 months after intervention. The marked decrease in the prevalence of goiters, in particular the larger ones, was also seen after 3 years of injection.

Iodized oil prophylaxis in mothers, before and during the first trimester of pregnancy, has shown improved psychomotor and intelligence quotients in offsprings.<sup>23-25,31</sup> It has been shown that iodized oil administration in children with severe iodine deficiency improves auditory thresholds, 1 to 3 years after intervention.<sup>32</sup>

**Table 2. Serum concentrations of TSH and thyroid hormones before and 1, 2 and 3 years after iodized oil injection in both sexes**

	Sex	Before injection	Months after injection		
			12	24	36
Serum TSH (mU/L)	F	19.9±20.1	0.9±0.8 <sup>†</sup>	0.8±0.6 <sup>†</sup>	1.8±1.6 <sup>*†</sup>
	M	20.6±25.7	1.4±2.3 <sup>†</sup>	0.6±1.8 <sup>†</sup>	2.5±2.3 <sup>*†</sup>
Serum T4 (µg/dL)	F	4.6±2.1	10.8±2.8 <sup>†</sup>	9.8±2.5 <sup>†</sup>	9.5±2.1 <sup>†</sup>
	M	5.4±2.0	10.7±3.3 <sup>†</sup>	10.2±2.3 <sup>†</sup>	9.7±1.8 <sup>†</sup>
Serum T3(ng/dL)	F	167±47	160±40	185±37	150±23
	M	168±40	146±39	158±33	151±27

F: Female n=43, M: male n=42; \* P<0.001, Compared to 24 months after injection; † P<0.001. Compared to before injection

Studies have shown that oral administration of lipiodol before or during the first trimester of pregnancy normalizes thyroid function in newborn babies and mothers. Iodized oil during the first trimester of pregnancy had no

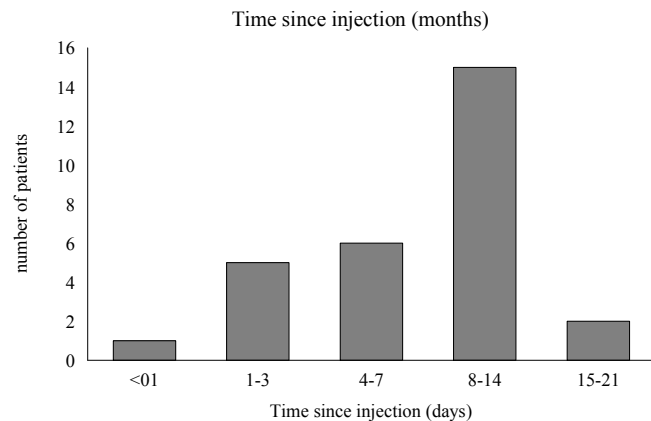
deleterious effects and may prevent hypothyroid or neurological cretinism. A decrease in both prematurity and stillbirth rates and the number of abortions was reported amongst the treated subjects.<sup>33, 34</sup>

**Route of administration:** Duration of the effects of iodine supplementation is much longer following intramuscular injection, as compared to that of oral administration of iodized oil. However, injections under field conditions in developing countries have disadvantages, especially the potential risk of communicable diseases and dependence on trained manpower. In this regard, oral administration of single doses of iodized oil capsules is a good alternative, since this requires less technical training, fewer instruments, and less time. Also, certain hazards are avoided, such as infections and improper disposal of needles.

**Complications of iodized oil administration:** Iodine excess, including the over correction of previous states of iodine deficiency, can impair thyroid function. Although a euthyroid individual can tolerate up to 1000  $\mu\text{g}$  iodine per day without side effects,<sup>35</sup> smaller doses below 500  $\mu\text{g}$  daily intake may cause adverse effects in a population previously exposed to iodine deficiency.

**Dermatological complications:** In a study of 3420 patients with simple goiter, skin complications were observed in 29 patients (0.8%), the highest incidence rate being observed in the 20-29, 30-39 and 40-49 year age groups.<sup>36</sup> The distribution of the patients with regard to the timing of dermatologic complications is illustrated in Fig. 2. Most of the complications were observed during the first 8-14 days after injection. Among the 29 patients with dermatologic problems, 4 had diffused, generalized lesions and 35 revealed only localized lesion at the site of injection.

**Iodine Induced Hyperthyroidism (IIH):** A rise in the occurrence of thyrotoxicosis has been reported in several endemics<sup>37-40</sup>, following reports of occurrence of IIH in two African countries.<sup>41,42</sup> Many prophylactic programs with salt iodization at various levels and with iodized oil in varying amounts have failed to demonstrate any increase in incidence of thyrotoxicosis.<sup>43-46</sup>

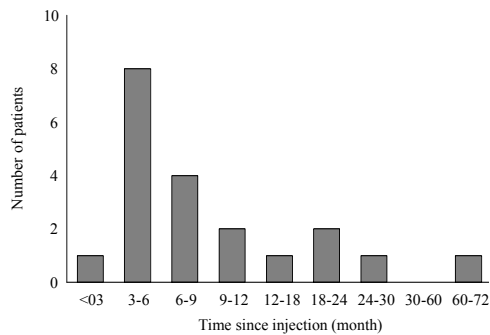


**Fig. 2. Time of occurrence of dermatologic side-effects following iodized oil injection. More than half of the cases occurred within 8 to 14 days following injection**

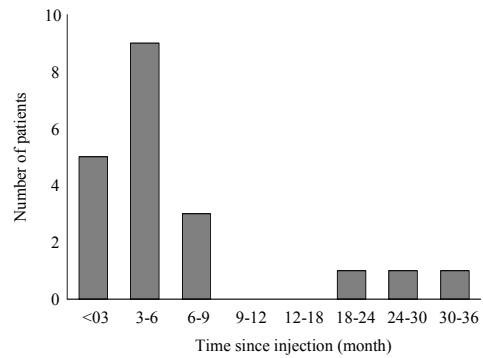
It has been suggested that IIH is rare in a well-executed IDD control program and the innumerable benefits that correction of iodine deficiency has in preventing brain damage, ensuring child survival and improving the learning abilities may be worth the risk of the rare occurrence of IIH.<sup>47</sup>

Table 2 shows the rare occurrence of proven IIH, both clinical and laboratory based diagnosis, reported in various studies. Many of the cases reported were transient and subclinical (laboratory increased T4 and/or T3 only). In the majority of studies the prevalence of IIH was 0.6-1.7%. However, there are many studies in which no IIH was reported. Time of occurrence of IIH is shown in Fig. 3. Following injection of 480 mg iodized oil to 3420 patients with simple goiter, 0.6% developed IIH; 12 of 20 patients were clinically hyperthyroid and 8 patients had to be treated with antithyroids.<sup>36</sup>

**Thyroiditis:** Some studies have suggested that excess iodine intake may trigger thyroid autoimmune reactivity by increasing the immunogenicity of thyroglobulin or by inducing damage to the thyroid cells by free radicals.<sup>48,49</sup> Cross-sectional studies of populations in Great Britain,<sup>50</sup> Italy<sup>51</sup> and Denmark



**Fig. 3. Time of occurrence of hyperthyroidism following iodized oil injection. Twelve out of 20 cases were detected within 3 to 9 months after intervention.**



**Fig. 4. Time of occurrence of hypothyroidism following iodized oil injection. Fourteen out of 20 cases occurred during first 6 months following injection, only 3 cases were detected after 9 months**

and Iceland,<sup>52</sup> have shown that the frequencies of thyroid autoantibodies and hypothyroidism are higher in iodine-replete than in iodine-deficient populations. However, none of the large epidemiological or clinical surveys following iodine supplementation have uncovered any significant iodine-induced thyroiditis with public health consequences,<sup>36,47,53</sup> and overwhelming numbers of subjects treated with iodized oil show no significant changes in antithyroid antibody titers.<sup>54,55</sup>

**Hypothyroidism:** A damaged thyroid may not be able to overcome the inhibitory effect of excess iodine. Transient and mild hypothyroidism are occasionally seen after iodized oil administration.<sup>57,58</sup> In the study of 3420 patients who received iodized oil injection,<sup>36</sup> hypothyroidism was observed in 20 patients (0.6%) with a female/male ratio of 9:1. Diffuse goiter was observed in 14 cases and nodular goiter in 6 patients, estimated thyroid size was  $34.5 \pm 5.3$  before and  $38.4 \pm 7.1$  g after injection (NS). Most cases of hypothyroidism were observed during the first 6 months after injection (Fig. 4).

**Iodine goiter:** The prevalence of goiter increases when iodine intake is chronically high. This condition has been reported in the

coastal areas of Japan and China and may accompany hypothyroidism.<sup>59,60</sup>

**Sialadenitis:** Mammary tissue, salivary glands, gastric mucus and choroids plexus, all of which have the same or a very similar symporter, concentrate iodide by a mechanism similar to that of the thyroid gland. Excess iodine may affect the salivary gland and cause iodine-induced sialadenitis or iodine mumps; 3.5-24% of those receiving iodized oil may develop transient sialadenitis.<sup>54,62</sup>

**Iodized oil in pregnancy:** Iodized oil has successfully been used for prophylaxis of iodine deficiency during pregnancy. There are no hard data to show that concentration of circulating iodine reaches the minimum inhibitory level for thyroid function. In a large study of 277 cord blood samples and 1026 blood samples of neonates and infants in Iran, whose mothers had received iodized oil injection during pregnancy, no case of hypothyroidism was detected.<sup>63</sup>

The use of iodized oil is recommended in remote areas of iodine deficiency, in the beginning of IDD control programs when iodized salt is not widely available and in areas where universal salt iodization has failed. The benefits of iodine supplementation outweigh its risks. When compared to the number

the number of doses given, the side effects occurring from the use of iodized oil for iodine deficiency are too rare to pose any significant obstacle to its continued use. Studies

have shown that the use of iodized oil during pregnancy is safe for the mother, the fetus and the neonate.

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